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## Original Communications.

### THE TREATMENT OF THE SUMMER DIARRHEAS OF CHILDREN.


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It is the object of this paper to consider the treatment of the condition commonly known as summer diarrhea of children. It is sometimes known as gastroenteritis or mycotic diarrhea. The most appropriate name is that adopted by Holt, acute gastroenteric intoxication. Symptoms and pathology are referred to only as required in explaining the reasons for treatment. It should be clearly understood at the outset that in diarrhea of this type, in the earlier stages at least, we are not dealing with an inflammatory condition, but with an acute intoxication. By intoxication we mean in modern medicine the absorption of poisonous ptomaines from a putrefying source. The bacteria do not enter the blood, but their toxins do. They are active poisons and produce conditions similar to those resulting from repeated alkaloidal injections. The symptoms depend upon the frequency or intensity of the dose injected or absorbed. The germs producing the intoxication in summer diarrheas have their habitat in the intestinal tract. They rarely enter the blood and do not generate there. The disease results from the absorption of the ptomaines alone, and is, therefore, not a septicemia nor an inflammatory condition. In the later stages, inflammation sometimes arises from irritation of the mucous membranes by acrid secretions or poisons. In the earlier stages we have to do simply with an intoxication. This statement cannot be too strongly implanted in the mind of the practitioner, for upon its realization must largely depend successful treatment.

The child with summer diarrhea is suffering from intoxication or arrest of digestion, either one or both. The arrest of digestive secretion very early in the infection is a most important factor. The power of digestion is annulled. By the time the physician makes his first visit, Nature has already taken the case in hand by emptying the stomach and bowels and taking away the appetite for food, which would add fuel to the flames. It is the wise course of the physician to follow the path pointed out to him. Four general measures of treatment, therefore, are indicated: Mechanical, dietetic, hygienic, and medicinal. Although a considerable proportion of space will necessarily be devoted in this article to other measures, it cannot be too strongly insisted that dietetic treatment is the most important.

At the outset, mechanical measures are usually indicated to clear the digestive tract of fermenting material. Stomach washing is rarely necessary, but should be resorted to should the child continue to vomit curds or food or sour and putrefying matter. Liberal drafts of warm water are usually well taken by the patient and obviate the necessity of the stomach tube. Rectal irrigation by means of a catheter or long tube is usually advisable; warm saline solution or boiled water with borax is to be used. Strong antiseptics are unnecessary and unsafe. Prompt unloading of the lower bowel by means of irrigation is very important. High irrigations are valuable until convalescence is thoroughly established. One thorough irrigation a day is more effective than many rectal injections. In the late stages, when the child has been depleted by large watery stools, it is well to leave as much water as possible in the colon for absorption.

Two facts indicate very clearly the line of dietetic treatment. First, digestion is at a standstill; second, the food, be it ever so perfect, is prone to become infected in the digestive tract and continue the fermentation. The old illustration of fresh milk in a sour bottle, cannot be too frequently repeated. Be the milk or the food ever so fresh and perfect, it will undergo putrefaction when brought into contact with putrefying matter.

The indications for feeding, therefore, are clear. First, keep all food out of the digestive tract as long as possible; second, in resuming the food, select that food capable of the least chemical change and putrefactive action. The changes in the food may be either fermentation of the carbohydrates and hydrocarbons, or putrefaction of the protein elements. Therefore, milk should be positively interdicted in summer diarrhea. It is true that milk is an admirable food for children. It is also true that beefsteak and potatoes are an admirable food for adults, but when the adult is stricken with fever, diarrhea, and vomiting, the beefsteak and potatoes are eliminated from the diet. The reasons for eliminating milk from the diet of the child under similar conditions are equally strong, but do not seem always to be recognized by practitioners.

At the outset of an acute diarrhea, therefore, all food should be prohibited, but water should be given freely, unless it induces vomiting. Even if a part of it is vomited, it is best to give some, for a portion may be retained and aid in preventing depletion of the tissues by excessive watery stools.

meral head and glenoid process, shown by the x ray. These changes have been found frequently and have been variously interpreted. Küstner believed they were due to epiphyseal separations with displacement of the diaphyseal fragment forward or backward. We are practically all agreed now that we are dealing here with dislocations in most cases and that they are practically all posterior. The evidence in one of von Bramann's cases, if I may be permitted to express an opinion, is strongly in favor of a traumatic origin at birth. There was at birth a fracture of the surgical neck of the humerus on the opposite, the right side, and positive evidence of injury on the left side, which was found palsied soon after birth. The humerus was also in marked internal rotation and the forearm pronated. One would infer from the report that von Bramann first found the dislocation on this side when the boy was thirteen years old. Our greatest need now is careful examination, by competent observers, of these shoulders immediately after birth. I believe that we shall soon obtain this, now that attention is being directed to these shoulders.

SUMMARY.

I should summarize briefly my reasons for believing that most obstetrical palsies are of shoulder joint origin, as follows:

1. In all of my cases in which the parents could recall the facts, their testimony was that following birth the children cried violently when the affected shoulder was manipulated.

2. Dr. J. W. McConnell, who has examined most of my cases, did not find abnormal electrical reactions in any. Fairbank, who reported forty cases, found that electrical examinations were not advisable before the end of the second month, when an anesthetic was essential, and that by that time the signs of recovery would render electrical examinations unnecessary. Sherren did not test the electrical reactions until the end of the third month. The exact electrical findings in reported cases are probably very rare. I cannot recall one.

3. All of my cases without subluxation ended in complete recovery, except one with some restriction of abduction and external rotation at the shoulder and an old injury at the elbow, and another about six months old, which is rapidly improving. All my cases in which there seemed to be a permanent palsy, showed posterior subluxation of the shoulder joint.

4. The chief evidence supporting the plexus theory, is that obtained at operation on the plexus, all of which can be explained by the joint lesion, except the actual rupture of the roots found in a few cases which, I believe, need further confirmation.

5. The frequent occurrence of posterior subluxation of the shoulder joint was not taken into account by those most favorable to the plexus theory.

6. The presence of the bent down condition of the acromion, in my opinion, will establish the occurrence of the subluxation at birth and, therefore, the dependence of the palsy upon the joint lesion.

7. Since the roots of the plexus are all mixed motor and sensory nerves, sensation should be frequently and seriously disturbed if the cause is a rupture of the plexus; yet sensation is rarely disturbed.

8. The Duchenne-Erb type of paralysis is generally agreed to be common to the frequent adult cases and the obstetrical palsies. The plexus lesion and the muscles paralyzed are agreed to be the same in both groups, yet the very frequent posterior subluxation in the obstetrical palsies, accounted for by the effects of the paralysis, never occurs in the adult cases. Why not the same effect from the same paralysis in both groups?

9. It is well known that traumatic dislocations of the shoulder frequently precede the paralysis in the adult cases, yet according to the present day supporters of the plexus theory, the dislocation in the children always follows and is due to the paralysis. Why this important difference? The establishment of a traumatic origin at birth would clear up all the difficulty.

10. Duchenne, who first described obstetrical palsies and ascribed them to injuries of the brachial plexus, found these posterior dislocations frequently associated. He said that many of them were due to the manipulations of the physician during delivery, i. e., they were traumatic in origin and occurred at birth.

In my opinion, the plexus theory is the greatest obstacle to the complete recovery of most of these cases, and if these dislocations were recognized at birth and completely reduced, there would be few permanent obstetrical palsies.

2005 CHESTNUT STREET.

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## TRANSPLANTATION OF A TESTICLE FROM THE DEAD TO THE LIVING BODY.

*Suggestiveness of Results in Their Relation to the Etiology and Treatment of Psoriasis, Carcinoma, Etc. (A Preliminary Report.)*

BY G. FRANK LYDSTON, M. D.,
Chicago.

Encouraged by certain results of sex gland implantation, a full report of which has for some time been in the hands of the editor of the NEW YORK MEDICAL JOURNAL and will shortly appear, I recently made an additional experiment which led to some very interesting observations. As noted when the paper referred to is published, I arrived at the conclusion from the apparently logical effect of my earlier implantations that obstinate chronic skin diseases, notably psoriasis, were a promising field for the therapeutic administration of the sex gland hormone via implantation.

The idea suggested itself that perversion of nutrition, primarily due, perhaps, to an abnormal quality and quantity of internal secretion from the sex or other glands—underlay skin lesions of the class in question. The obvious inference was that cell stimulation by the sex hormone would be found to prove beneficial. Reasoning from the effect upon skin nutrition which I had observed to follow sex gland implantation, I concluded that chronic disease might be benefited by implantation of sex glands. Inasmuch as the sex gland most powerfully stimulates the nutrition of the skin,

probably also the action of other internal secretory glands—it would seem logical to infer that a similar action might be expected in other tissues.

In my paper which is shortly to appear I have suggested that arteriosclerosis, chronic renal disease, diabetes, tuberculosis, and even carcinoma, and numerous other conditions involving perverted cell structure and function, may offer a suitable field for the use of sex gland hormone—notably by implantation. The germ theory of the etiology of carcinoma has not seemed to me well grounded. Indeed, I am of opinion that the nearer we come to a perfect knowledge of the internal secretions, the nearer we will be to the true etiology and rational therapeutics of carcinoma. In any event, whatever the abnormal impulse may be, the result is perverted cell growth, and we may at least regard hopefully any remedial measure that promises improvement in cell nutrition.

To put my view of the etiology of malignant disease concretely: I believe that there is more than a chronological coincidence in the association of sarcoma with childhood and youth and of carcinoma with later life. A disturbance of cell nutritive equilibrium from perverted quantity or quality—or both—of internal secretion—probably of the sex gland, the thyroid perhaps playing an important part—in my opinion underlies both varieties of malignant disease. The sex gland hormone theoretically should restore this equilibrium, making in effect the cells of the sarcomata older and stronger and those of the true carcinomata younger and stronger.

In the light of the foregoing view of malignant disease, the theory of Cohnheim is especially apt in its application to malignant disease of early life, and to sarcoma and the softer varieties of carcinoma at any age.

The association of cancer with the approach or occurrence of the menopause, and with advancing age in the male, is suggestive of change in the sex gland hormone as the chief underlying factor. Epithelioma of the skin especially may be compared to psoriasis in that a defect of nutrition due to perversion of internal secretion and localized by special factors of irritation is a reasonable underlying

role of microorganisms in carcinoma may be merely that of a special determining perverted cell growth through the irrita- luced, and no more specific than trauma- ch so often appears to be the point of de- malignant disease. Thyroid extract has l to have cured psoriasis. This is not The thyroid and sex gland hormones are complementary. Thyroid defect ay be the more important factor in malig- se of early life.

due to defective quantity and quality of of both hormones, perhaps may be cured nd may require a combination of both. ning needful in thyroid implantation may aneous sex gland implantation. It is my tion that the administration of sex gland by implantation—with or without thyroid as events may prove—is the logical indi- d well worthy of trial in malignant disease. hether beneficial results will follow organo-therapy, this naturally will be determined by many factors independent of the etiology of the disease.

Case. Man, aged fifty-three years, musician, consulted me June 10, 1914; hard drinker and a gourmand; no history of syphilis; Wassermann negative; history of two tappings for ascites, six years before. A diagnosis of cirrhosis of the liver was made at that time. When the patient first consulted me, his abdomen was enormously distended with fluid. Jaundice had appeared a few days before and had become quite pronounced. No pain was complained of, nor was there any history of pain previously. The subject was very weak and markedly incommoded by the enormous bulk of his abdomen. His appetite had been excellent until a few days before, since when it had failed. June 14th, I removed nearly six gallons of bile stained transudate from the abdominal cavity, affording the patient great relief. The liver was found to be greatly enlarged and hard. The gallbladder was greatly distended and its walls much thickened and hard. In the left iliohypochondriac region was a hard, elongated tumor mass extending downward from the under surface of the liver for about four inches. This tumor might have been renal or even omental. It could not be definitely determined that it was attached to the liver. The tumor seemed probably malignant. There was a good sized umbilical hernia, evidently containing only fluid, which freely flowed back and forth under pressure. This had been unsuccessfully operated upon. The urine contained bile in large amount and a small quantity of albumin, but no casts.

The patient's heart was very weak following the operation and strychnine was given hypodermically for several days. On the backs of the arms and forearms, the front of the right leg, the buttocks, the lumbar region, and the back were large patches of typical psoriasis from which the patient had suffered for many years. A patch of psoriasis of the size of the palm of one's hand existed on the abdomen, involving a small portion of the skin covering the umbilical hernia.

On June 19 I implanted in the patient's right scrotal sac a testicle—with the epididymis excised—removed from an apparently healthy subject about twenty-one years of age, dead thirty hours before from contact with a live wire. The operation was done ten hours after removal of the testis from the dead subject—i. e., forty hours after death. The postoperative course was uneventful. The wound healed by primary union and there was very little swelling about the site of the implantation. The highest temperature recorded was 100° F. Today—the eighth day—the implantation *per se* would seem to be successful.

On the third day after the implantation improvement was noted in the psoriasis. At present writing, the eighth day after operation, the lesions are so improved that they scarcely can be recognized as psoriasis. The skin over one elbow is nearly normal. The patches upon the back have entirely disappeared. The jaundice has improved, the blood pressure—which was low on acount of the patient's debilitated condition—has increased, the pulse is perceptibly stronger, appetite has greatly increased, the hemoglobin, which was approximately sixty per cent., is now seventy per cent., and there is a distinct improvement in color, aside from the lessening of the jaundice. A considerable reaccumulation of fluid has occurred and a second tapping probably will become necessary.

I submit without further comment this brief preliminary report of the foregoing results of the primary or initial dose of sex hormogene. What I have to say of sex gland hormone therapy in general will, I hope, shortly appear in this Journal.

32 North State Street.

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## Original Communications.

### IMPLANTATION OF THE GENERATIVE GLANDS AND ITS THERAPEUTIC POSSIBILITIES.*

*Successful Autoimplantation of a Testis from a Subject Dead Twenty-four Hours. Other Successful Implantations of Testes and Ovaries from Dead Subjects. Experimental Implantations in Various Conditions, and Cross Implantations of Testes and Ovaries Taken from Dead Subjects.*


BY G. FRANK LYDSTON, M. D.,

Chicago,

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Since long before the days of oophorectomy craze —the darkest blot upon the history of the surgery of the last quarter of the nineteenth century—the attention of the profession has been more or less insistently directed to the possible relation of various derangements of the sex glands to certain morbid phenomena of a general or special character, notably affecting the nervous system. The interest aroused finally led to the widespread adoption of the Battey operation, which once was so disastrously fashionable as a remedy for "neuroses" in women.

The period at which I myself first began to suspect that in many cases we were on the wrong track, is fairly well fixed in my mind by two personal cases that occurred during the then prevalent epidemic of ovarian mutilation into which the masters of surgery had led us. These cases were respectively one that now probably would be termed dementia præcox, in a girl of twenty years, and another of "hysteroepilepsy" in a girl of eighteen. In the former I set about removal of the ovaries to relieve the "reflex irritation" which, according to the then fallacious popular theory, presumptively underlay the nerve and brain symptoms, and was astonished to find "atrophied"—or more probably, undeveloped—ovaries and uterus. In the other case, operation was refused and, several years later, I had the opportunity of making an autopsy, the young woman having died peacefully without surgical interference. "Atrophied"—undeveloped —ovaries and an undersized uterus again were found. Both subjects had menstruated, although tardily and irregularly from the beginning, but finally menstruation had entirely ceased.

Even at that early period of my professional career, these cases suggested the possibility that an aberration of function of the ovary, rather than reflex irritation from diseased ovarian structure, had an etiological relation to some of the manifold nervous phenomena in women, for which bushels of ovaries were being sacrificed. In the light of recent researches in the field of internal secretions, it would seem that possibly the profession builded wiser than it knew in attributing to ovarian disease a host of nervous disorders in women.

It was a great misfortune that we then had no knowledge of the internal secretions, and no blood researches to show us that the trouble often lay, so to speak, not in too much ovary, but in what was, in effect, too little, the internal sex gland secretion being either insufficient in quantity or perverted in quality, from disease or congenital structural defect.

It is remarkable that the nervous and other phenomena following castration in females who previously were normal in respect to the nervous system, did not make matters clearer to the profession, but possibly our attention was distracted and our reasoning powers were inhibited by the grave discussions with which we were regaled on the wisdom of "leaving the ovarian nerves intact" when we removed the ovaries. Even this point in technic was regarded as important, chiefly because of the consideration of the influence of the ovarian tissue and the ovarian nerve upon menstruation, this function being regarded as the main factor in the preservation of a normal nervous system after extensive pelvic mutilations.

Since the inception of the pelvic mutilation fad, the profession has had the opportunity of observing the nervous effects of the Ramm-White operation of castration for enlarged prostate—now reposing so peacefully in the surgical dead lumber room by the side of the long defunct epidemic oophorectomy mania which, unhappily, still perverts the minds of a few of the surgically obscure and, what is worse, inspires the malpractice of certain commercially depraved members of the profession.

It is noteworthy that Brown-Séquard's self experimentation with the extract of the testes of lambs really signified more than either he himself or the profession comprehended. Had we grasped the great principle involved, the much ridiculed "elixir of life" probably would have been more of an epoch maker than a joke. Believing that a most important principle was involved in Brown-Séquard's self experimentation, I have for many years been especially interested in the problem of the normal


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equilibrium between sexual activity and age, and that between general bodily vigor and sex gland structural and functional integrity. The most fascinating, although, perhaps, the least practical phase of the problem, has been the question of the interrelation of senility and sex gland activity.

The association of remarkable sex vigor with notable longevity is a matter of common observation, even among laymen, but which is the *propter* and which the *post*? Do we age because the sex glands deteriorate or do they deteriorate because we age? As shown by his report of his experiments upon himself with the juices of sex glands of the lower animals, Brown-Séquard evidently had certain ideas of his own upon the subject. Is there merely a normal, very delicate equilibrium between age and sex gland activity, the maintenance of which determines whether or not the individual will live and preserve the vital functions, notably the sex powers, in active condition to the normal extreme age average? Finally, while assuming as skeptical an attitude as we please toward the possibility of the discovery of the "elixir of life," may we not—granting the acceptance of the "equilibrium" theory just suggested—logically search for a method of restoring or preserving that equilibrium, thus prolonging life to its rare, normal conclusion of extreme old age? May we not even hope to go beyond the limit of what we now regard as "extreme"? Obviously, the collateral problems suggested are very numerous.

At first sight the logical answer seems to be that sex gland activity is entirely dependent upon age and general nutrition, becoming impaired *pari passu* with advancing age, to be finally extinguished by the degenerescence of senility. In the light of our present knowledge of the internal secretions, however, are we not justified in suspecting that rejuvenation of the supply of internal sex gland secretion may have a marked effect in retarding age, the disturbance of equilibrium being in favor of the individual supplied with the gland elements necessary to the formation of young internal secretion? Admitting the cogency of this theory, who could foretell how far longevity might be prolonged by successive supplies of young internal secretion? We, of course, must admit that anatomical and physiological machinery is predestined to wear out, and whatever one may think of the future prospects of spiritual man, we must recognize his mortal limitations. If ever we discover the fountain of youth, we are likely to find that its waters will be doled out to us very sparingly.

Following the widely heralded alleged discovery of the "elixir of life" by Brown-Séquard, came a host of imitators. These were of two classes: First, ethical workers in therapeutic fields; second, quacks who pretended to employ animal extracts. Among the latter was a distinguished American neurologist, since dead, who prostituted to commercialism a once enviable reputation. His testine and cerebrine will be recalled by many of the older members of the profession. Samples submitted to me direct by the neurologist aforesaid proved to be merely solutions of glonoin.

Since the publication of Brown-Séquard's experiments, and more particularly since the discovery of the internal secretions, the profession has been deluged with animal extracts of many kinds, manifold pretensions, and varying degrees of harmfulness and therapeutic efficiency. Naturally, much attention has been paid to sex gland extracts. These I will give scant courtesy. In my opinion, most of them, up to date, have been wrong in principle, toxic in action, and absolutely valueless, save as sordidly commercial propositions. Recently, however, some really scientific preparations have appeared and in some instances apparently have given brilliant results.

One of the unfortunate features of organotherapy is the toxicity of animal extracts in general; this with due deference to the brilliant results achieved by some of them. It is logical to assume, also, that the therapeutic potency of the best of them is not to be compared to that of the hormones produced *in vivo* and normally discharged into the circulation. Some of the various extracts of internal secretory glands probably bear the same relation to the internal secretions that old fashioned beef tea does to wholesome beef. The nutritive properties of the beef do not appear in the beef tea, but the toxic elements do. As to whether emulsions of fresh material will prove more satisfactory than "extracts" have done remains to be shown. The author is optimistic in this regard.

Since the attention of the profession has been so pertinently directed to the internal secretions, I have given considerable thought to the probable relation of sex gland secretory aberrations, first, to nutrition in general; second, to brain and nerve integrity; third, to sex power and activity; fourth, to senile pathology and physiology. The impression that the well being of all animals hinged upon the integrity of the sex organs, and especially of the testis and ovary, prevailed in very ancient times. The mechanism by which the sexual apparatus operates was enveloped in mystery until we began to comprehend that the procreative function of the sex glands was not their only biological mission. The phenomena which for centuries were known to take place after suppression of the secretion of the sexual glands by castration, and by the physiological change incidental to the climacteric, were formerly supposed to be due to "reflex nervous action." It was noted that the sexes were much alike in this respect, and it has long been suspected that the male has a climacteric, analogous to that of the opposite sex, which occurs later in life than in the female, and is attended by varying peculiarities of nerve action. As this is likely to occur in the male long before fertility ceases—if, indeed, we accept such a climacteric at all, as I am inclined to do—the only rational explanation, in the light of modern research, seems to be a diminution or change, or both, in the internal secretion of the sexual glands, with, of course, due appreciation of arterial changes, which themselves may be merely secondary. Still more logically will this theory explain the nerve phenomena of the menopause.

In the latter part of the eighteenth century, Bordiu (1) asserted that the nervous and other morbid phenomena which followed removal of the sex organs, and in diseased conditions affecting them, were due to either a deficiency or superfluity of the

procreative glandular secretions. Bordieu, however, had no conception of internal secretions. Johannes Müller (2) recognized certain "ductless" glands. He even designated the placenta as a ductless gland. These glands, he believed, modified the blood which circulated through them, and thereby gave what he called a "plastic influence" to the generative circulation.

The testicle long has been known to have a double function, but until recently none knew that both functions were secretory. That it acts as a duct gland has been accepted as long as its physiology has been known. In 1849, Berthold (3), of Göttingen, transplanted the testes of cocks to their abdominal cavities and showed that the masculine sex qualities were preserved, through, he averred, an effect upon the blood. Thus, without precise scientific knowledge, and with no accuracy of nomenclature, Berthold first proved the existence and significance of what we now recognize as an internal secretion. Many years later, Forel (4) asserted that "the implantation of a sex gland in any part of the body is sufficient to arrest the production of the special peculiarities of the eunuch," and he might have added, also, of the amazon.

Since Berthold's day, and especially of recent years, considerable experimental work has been done in sex gland implantation, some of which had in view merely transplantation *per se* and some the matter of internal secretion in mind. A number of the contributions are worthy of special mention. Herlitzka (5), in 1899, reported successful experimental transplantations of testes of frogs into the peritoneal cavity of the same individual. Later, Meyns (6) successfully transplanted portions of frogs' testes into the dorsal lymph vessels. Hammond and Sutton (7) reported a case of testicle transplantation. A testicle was removed from a subject who had just died of traumatic hemorrhage, due to a rupture of the liver, and placed in sterile salt solution in cold storage. A sarcomatous testicle was removed from a patient, twenty-nine and a half hours later, and the testis from the dead body systematically anastomosed upon the cord stump. Healing was perfect. One month later, only a small nodule remained on the end of the cord. Some time later this was observed to have enlarged a little, whether or not from return of the sarcoma has, I believe, not yet appeared. The object of the transplantation was a purely psychic effect, and no observations regarding sex hormone therapy were made. This case obviously was a severe test of implantation on account of the possible, or even probable, malignant involvement of the cord. Be it remarked that a testis removed from a body immediately after death is the equivalent of one taken from the living subject.

Foà (8), after extensive experiments on animals, concluded that testicle grafts fail, merely because of the impracticability of reestablishing, by any technic then known, blood and nerve supply. Guthrie (9), however, found that a testicle removed from a fowl and planted in the shoulder of the same bird, was growing, had considerably enlarged, and had acquired a liberal blood supply after four months. He also concludes from his experiments that "ovarian tissue" from fowls engrafted into fowls may develop and preserve its functional powers to a high degree." Cevolotto (10) found that, after forty-five days, small pieces of testicle tissue implanted under the skin of rabbits showed changes which proved that the highly differentiated cells of such tissues tend to retrograde to ordinary connective tissue cells. He notes an increase of Sertoli cells as an evidence of degenerescence of the gland tissue proper. In this far, Cevolotto is pessimistic regarding the success of sex gland transplantation.

Lode (11), following Berthold, believed he had proved by experiment that testes of fowls transplanted beneath the skin retain their vitality and functional activity, continuing to secrete semen. He also concludes that, in fowls at least, a special secretory nerve supply for the testes does not exist. Foges (12), from his experiments on fowls, concluded that, while the semen producing power of transplanted testes was preserved, their influence on the secondary sex characteristics was not. This latter observation does not accord with the results of certain recent experiments on fowls by the author, although, as to the end results, it is too early to arrive at definite conclusions.

Ribbert (13) holds that he has shown by animal experimentation the feasibility of transplantation of various living tissues, the terminal results not being uniform for different tissues, and resorption finally taking place in all tissues save the epithelial structures of the skin and conjunctiva.

The gross results of caponizing fowls are familiar, even to the laity. In a series of recent experiments on fowls, I made some interesting observations of the effects of glands from nonrelated birds, implanted in the capon. The nutritive stimulant effect was remarkable.

Guthrie (14) reports an experiment in which removal of the ovaries resulted in the development of secondary male characteristics, the subject when grown being spurred, plumaged like the male, pugnacious to cocks, and treading hens as would a cock. I have owned a number of supposedly normal hens —never experimented upon—which were spurred, given to crowing, pugnacious to strange cocks, and who would assume charge of the flock of hens and tread them systematically, as soon as the cock was removed from the run. Despite their "inversion" symptoms, these hens were good layers and their progeny was normal. Dr. A. E. Brown, of Waukegan, Ill., had in his possession at one time, a hen bred by me which he reported as having had the characteristics mentioned. Such hens are familiar to most breeders of domestic fowl.

Apropos of plumage as a criterion of secondary sex characteristics in fowls, I take the opportunity of observing that it is not so important as might be supposed. The hencock, or "hennie," is familiar to all game fowl fanciers. The plumage of the male is practically the same as that of the female. These fowls are vicious fighters, some strains are heavy weights, and all are excellent layers and breeders. The hencock often crops out either as a sport or a throwback (atavism). An observation of my own may be of interest. For ten years I had bred a certain strain of brilliant colored, rich plumaged, black red game bantams. The originator

of the strain had bred them for twenty-five years. Neither of us ever had made an outcross, but carefully preserved the type by inbreeding and line breeding. Desiring to increase the vigor of the stock by a change of environment, I placed some of these bantams—a full brother and several sisters—in the hands of Mr. Walter Adams, a very careful breeder, of Hubbard Woods, Ill. In the second year thereafter, four fine specimens of hencock appeared in the progeny. These I succeeded in perpetuating fairly well by careful selection—a difficult task because the female hennie could not be distinguished from her "regulation" sisters.

Claude Bernard(15), in 1855, called attention to the glycosuric function of the liver as dependent on a special internal secretory action under control of the nervous system. Brown-Séquard (16), in 1869, first expressed the idea that all glands, whether with or without ducts, supplied to the blood a substance a deficiency of which produced pathological disturbances. It was not, however, till the publication of his celebrated experiments on himself that attention was given to the question of internal secretions. In 1889, at the age of seventy-two years, he injected himself with testicular extract from the lower animals. According to his reports, he experienced a marked improvement in mental activity, physical strength, and bowel action, and an increased appetite.

Poehl (17) states that "injections of spermine have been given to enfeebled old men who had lost appetite and sleep, and produced improvement lasting for months. From the instances given, I have selected that of an old lady of ninety-five years, afflicted with severe sclerosis of the arteries, with no appetite, a bad digestion, and constipation. This patient had complained for several years of sacral pains, and, moreover, was nearly quite deaf and suffered from periodical attacks of malarial fever. The injections of spermine, given for a period of fifteen months, restored the old lady to such an extent that she recovered her power of hearing and felt the sacral pains only slightly and after a long walk. Her general condition was highly satisfactory."

Brown-Séquard's self experimentation is generally recognized as the pioneer work in organotherapy. The suggestion of the old humoral pathology, fathered by Bichat, and of the once derided alleged vagaries of Hahnemann, which lingers about the physiology and pathology of the internal secretions and vaccinoserotherapy, is striking, and should appeal to the modesty of modern science. It shows how close the great thinkers of past generations came to the solution of problems which a better knowledge of chemistry, biology, and bacteriology would have made clear.

Bayliss and Starling (18) proposed the name *hormone,* meaning to awake or excite, for the substances contained in those internal secretions that affect the functions of other organs. It appears that continuous doses of some hormones are necessary to maintain physiological activity at par. Presumptive evidence of this is shown by the physiological hypertrophy of the remaining gland when one of a pair is removed or destroyed. In the case of duct glands, this, of course, bears upon the ordinary secretory function, as well as upon that of internal secretion.

That the internal secretions are therapeutically powerful is shown by the brilliant results obtained from the administration of thyroid extract and implanted thyroid fragments in cretinism and allied conditions due to pathological disturbances or removal of the thyroid, and by the more recent observations on pituitrin and other extracts. That the preservation of a very small portion of thyroid tissue in thyroidectomy will prevent serious afterresults has been abundantly proved. This latter observation is also true, although perhaps in less measure, of the ovary and testis. Paschoud (19) also has published some remarkable results from thyroid grafting.

According to Biedl (20), the hormones do not provoke the formation of antibodies. It would appear, then, that any increased resistance to infections that may result from them when used therapeutically would, of necessity, be indirectly produced through such stimulating or tonic effect as they might have upon the organism in general. The question of whether resistance to infection can be dissociated from the formation of antibodies is, of course, not under consideration here.

Schiefferdecker's hypothesis of the physiological action of the specific internal secretions is very interesting, in that he advances a direct nervous intervention as a substitute for the old theory of reflex action. He says (21): "Internal secretion determines the effect which the products of metabolism, excreted by the nerve cells during the simple processes of nutrition, will exercise upon other nerve cells or upon the cells of the end organs, such activity being called 'trophic.' It also determines the effect which the products of metabolism excreted in the course of specific activity will produce, and this effect is known as 'irritation' or 'stimulus.'" I will not argue the point of whether "irritation" and physiological "stimulus" are the same. The distinction seems too obvious.

The wonders of even the generative sex gland function are almost incomprehensible to all but the scientist, who has come to accept them as a matter of course. At birth the ovaries contain something like seventy thousand ovules, only 360 of which mature and discharge during a normal menstrual life of about thirty years. The real meaning of this is staggering. The intrinsic capacity of development into a new being under favorable conditions may be assumed to be theoretically possessed by each and every one of these ovules, and we surely must grant creative potentialities to the 360 ovules which mature and are discharged from the ovary. Every one of these mature ovules, fertilized and transplanted to a favorable soil, would develop into a new being. And the fertilized ovum seems indifferent to its feeding ground, whether peritoneum, Fallopian tube, or endometrium. The embryo could come to maturity on each of them, were the purely mechanical conditions favorable. Living blood—if it is not alien—with the complex biochemical products that it contains, alone is necessary. The local source of the blood matters but little.

The kinetic energy of the spermatozoon is remarkable, and the movements thereby rendered possible

are very active. It can traverse its own length in one second, an inch in seven and a half minutes, and the distance from the ostium vaginæ to the cervix in about three and a half hours. The zoosperm is indifferent to somatic death until long after its occurrence. Living sperm cells are found in the vagina eight days after coitus, and have been found in the Fallopian tubes three and a half weeks afterward. Three days after the execution of a murderer, living spermatozoa were found in the testes. In the female bat they live for months, and in the queen bee for three years. They have been kept alive for three days in a culture oven.

The marvelous nutritional and formative potentialities of the generative secretional products of the sex glands are proved by the results of the combination of the spermatozoid and the ovule. The combination of a cell measuring only 1/500 inch in length with another cell measuring 1/125 of an inch in diameter produces a germ which requires only a proper environment for its development into a new being. Comprehension of this wonderful biological fact alone should be sufficient to enable us to appreciate the possibilities of sex gland secretion in therapeutics.

Both the spermatozoid and the ovule seemingly must depend inevitably upon the internal secretory function of the glands which produced them for the remarkable results following their combination. The internal secretory function of the testis and ovary possibly may in no wise be dependent upon the generative glandular mechanism, but it is hardly conceivable that either spermatozoa or ovules of normal constitution can be formed independently of the local and general nutritional stimulus produced by the hormone.

What is it that imparts the formative energy to spermatozoid and ovule if it is not the internal secretion acting through the medium of the blood, or directly upon the procreative glandular tissue—or both? The union of sperm cell and ovule merely serves to make dynamic the potential cell energy of each. The combination surely develops a powerful nutritional stimulus. It is by no means improbable that the quality of progeny depends on the quantity and quality of the internal secretion, both before conception in both sexes and after conception in the female. Why may we not hope to improve heredity, or even determine sex, by the employment of internal secretion through the medium of sex gland implantation or other methods of administration? What may we not accomplish therapeutically with the vital energy of glandular organs which produce such powerful biological elements as the ovule and spermatozoon and in such large quantity throughout life, if only we can make that energy do our bidding, as seemingly we can?

While the double secretory function of the generative glands has for some years been conceded, the existence of specially differentiated histological secretory elements in these important glands has not been so generally accepted. Certain investigators, notably Nussbaum (22), have held that the generative elements of the glands produce the hormone. Others, again, have contended that there is a double set of secretory elements, one of which elaborates the internal secretion and the other the generative secretion proper. The problem appears much simpler in the case of the ovary than in that of the testis.

Prénant (23), Born (24), and Fraenkel (25) showed that the corpus luteum is epithelial in structure and possesses an internal secretory function that is independent of the generative function of the gland. Bouin (26) held that he had demonstrated that the testis contained, not only the obviously important seminiferous tubules, but also other morphologically differentiated elements of great biological importance from a secretory viewpoint. Nussbaum (27), after a series of experiments on frogs, concludes that the influence of the testes on sexual desire and function is biochemical and acts, not only with the glands normally attached, but also when the testes are isolated by cutting off their nerve attachments.

Lespinasse (28), before the genitourinary section of the American Medical Association in June, 1913, reported a case of impotency cured by "slices" of testis, one mm. in thickness, taken from a living subject and immediately transferred to the scrotum and rectus muscle of a subject who had been castrated. On the fourth day desire and power of erection returned, and had persisted for two years when the patient was last seen. The same author reports a second case of impotency treated by implantation in the scrotal sac of a portion of testis from a living body (29). Lespinasse's interesting experiments in the already familiar field of transplantation of fragments of sex glands from the living to the living, bore no reference to the broad general subject of hormone therapy—save as regards virility—or of transplantation of sex glands from dead subjects. He notes, however, the probable preservation of the interstitial internal secreting tissue as the explanation of his results.*

Loisel (30) showed by experiment that the testes and ovaries of both warm and cold blooded animals contained toxic substances which produced serious symptoms and even death, when injected into frogs and rabbits. This, however, merely proves the existence of toxic materials in extracts made from the generative glands, and, so far as it goes, in general explains the frequent disappointments and occasional harm of using therapeutically extracts from these tissues. In the author's opinion, Loisel's observations have no bearing on the action of the physiological internal secretions of a successfully implanted sex gland.

That the mere passage of the spermatozoa is not necessary to secondary sex characteristics has been amply proved by experimental, accidental, and pathological mechanical sterilization, i. e., sterilization which does not destroy the spermatozoa-producing function of the testis, but merely prevents their exit from the gland. Obviously, however, and without questioning the fact that there is a double secretory function of the testis, this alone does not prove that the spermatic secretory tissue proper is not wholly or partially responsible for secondary sex characteristics, for spermatic secre-

*The implantation of slices of testis practically is a repetition of Leo Loeb's culture of tissues within the living body, reported in *Johns Hopkins Hospital Bulletin*, 1898, and *Proceedings of the Society of Experimental Biology and Medicine*, viii, 1911, and *Anatomical Record*, viii, 1912.

tion and resorption still continue after mechanical sterilization. Still less does it prove, when taken alone, that the internal secretion is not elaborated and eliminated with the semen by the tubuli seminiferi, or that the tubuli are not necessary to perfect sex development. Neither does absence or nonformation of spermatozoids mean that the remaining elements of the semen are physiologically worthless. It has been shown that a very small amount of testicular or ovarian tissue is sufficient to preserve the secondary sex characteristics. This also does not prove the relative unimportance in this regard of the true generative tissue.

In brief, histological secretory differentiation having positively been demonstrated—and disregarding the spermatozoids—we still cannot by it alone exclude the secretory function of the true generative gland tissue from what I will term the sex cycle. The histological structure on which internal testicular secretion depends was termed by Leydig,[3] "between cells." Four years later, Kölliker described them. In 1903 they were termed by Bouin and Ancel (32), in an exhaustive treatise, *glande interstitielle du testicule*. These cells are situated in the interstitial tissue between the tubuli seminiferi and are of mesodermic origin. Hanes (33) says that the Sertoli and spermatogenic cells play no part in the internal secretion, the Sertoli cells supplying fat to the sperm cells, the internal secretion, in all probability being supplied by the cells of Leydig.

The physiological characteristics of these cells, and experimental work on animals by various investigators, suggest the possibility that, even where the spermatic tubules are "strangled out" of implanted testicular structure by subsequent destruction and replacement of generative glandular tissue by true connective tissue, the internal secretory function of the implanted gland tissue—and hence such therapeutic efficacy as it may possess—possibly may continue indefinitely.

My experiments show that the cells of Leydig actually proliferate, so that the remnants of successfully implanted glands contain relatively more interstitial cells than does the normal gland.

The facts that, first, the semen is not perfectly elaborated and the spermatozoa consequently are not perfectly formed until the seminal elements are acted upon by the epididymis; second, that destruction or removal of the epididymis does not affect the secondary sex characteristics, and, third, that secondary sex characteristics manifest themselves before either spermatozoa are formed or ovules matured, in a measure prove that the latter are not dependent upon the generative elements, but upon some special property of the glandular tissue of the sex glands. Moll (34) says: "If it be assumed that the testicles can secrete substances upon the influence of which the development of the secondary sexual characters depends, it is obvious that these substances have nothing to do with the spermatozoa, inasmuch as the testicles exert the influence under consideration at an age at which the formation of spermatozoa has not yet begun. The substances that act in this way must be of a different kind."

Marshall and Hammond (35), in experiments on sheep, conclude that castration checks horn growth (a secondary sex characteristic). Unilateral castration inhibits, but does not check horn growth. Removal of the testes without removal of the epididymes checks horn growth. The authors accept the hormone theory of development of secondary sex characteristics. They believe, however, that the role of the epididymis in hormone production is of little or no importance. This is not in harmony with the observations of veterinarians, who have held that preservation of the secondary sex characteristics after castration is due to failure to include the epididymes in the exsection. Cryptorchidism is, of course, another and a satisfactory explanation in some cases of inexpert castration. I have seen a supposed gelding repeatedly cover mares. This animal was said to have retained his sexual power because he was "castrated late."

It has been shown that the x ray destroys the spermatozoa producing function of the testis without affecting the secondary sex characteristics. The further observation that the x ray primarily destroys the spermatic glandular tissue, but does not affect the interstitial tissue, is held to show conclusively that the latter is the source of the all important internal secretion. A few tubuli escape the action of the ray, and regeneration of the testis has been shown to occur. The question arises, however, as to whether inhibition of the production of the delicate spermatic cells—spermatozoids—necessarily means that the generative gland tissue proper really is destroyed. Does not the so called "regeneration" mean a restoration of function? I do not believe that a regeneration of killed tubuli seminiferi is possible. We may profitably note what occurs in the orchitis of parotiditis, and reflect on how easily the gland is destroyed. It also should be noted, however, that when one testis is atrophied by parotiditic infection and the remaining organ subsequently is lost, the secondary sex characteristics are preserved. This I have observed in one case. It is quite as pertinent to the subject in hand as are the results of x ray experiments and accidents. Prolonged and repeated exposure to the ray will, of course, destroy the entire structure of the gland and produce effects similar to complete castration.

Summarizing all that is known regarding the internal secretory tissue of the testis, Biedl (36) says: "We are led to the inevitable conclusion that the hormone which gives to the organism its male characteristics is elaborated in the cells of Leydig, in the interstitial tissue. Despite their mesodermal origin, these cells are able actively to produce certain specific substances and to transfer these substances to the blood stream. Such being the case, we are justified in describing them as an 'interstitial gland.'"

As already hinted, I am not quite sure that Biedl's conclusion is "inevitable." It is by no means impossible that the procreative elements of the testis themselves have a double secreting action, the internal secretion being elaborated by the true secretory glandular tissue, and mainly taken up and distributed by the bloodvessels of the organ, the

excess escaping with the spermatozoa.[1] Consistently with this hypothesis, the internal secretion probably is constant, while the spermatozoa producing function is easily inhibited or destroyed, and the spermatozoa doubtless are more or less intermittently produced, varying with sex stimuli and demand. In brief, I am not inclined to the belief that the destruction of the spermatozoa producing function necessarily means destruction of the true generative gland tissue.

Biedl further says: "It is highly probable that, by the agency of its secretory products, this gland is responsible for the development of the male sexual gland from the differential genital tract. That it has a determining influence on the normal development and maturity of the generative portion of the sexual gland, the formation of the secondary genital organs, and the existence and persistence of those morphological and biological characteristics which are the property of the male sex, is undoubted."

The immediately foregoing positive assertion of Biedl's being accepted as in the main true, how can we reject as improbable the view that a successful testicular implantation should, other things being equal, increase virility—either by the direct action of its internal secretion upon the generative gland tissue, or (a) by entering the blood, improving general nutrition, and (b) returning to and acting as a stimulant, tonic, and nutrient reconstructive upon the generative gland cells? If the internal secretory tissue is the self elaborated "meat" upon which the generative tissue proper of the testis "feeds," aged and weakened glands should profit even by an increased supply alone; this, granting that an oversupply is impracticable—as probably it is. In connection herewith, it is noteworthy that advancing age and castration alike tend to the production of obesity. It should be noted also that obesity, even in relatively young subjects, is likely to be attended by comparative inactivity of sexuality.[2]

From the viewpoint of its internal secretory function, the ovary is very similar to the testicle. The correlation of the physiological function of the Graafian follicles and of the corpus luteum has long been well known. The function of the stromal gland cells, however, has attracted attention only in recent years, Regaud and Policard (37) being the first to suggest that these glandular cells might be secretory. Bouin (38), in 1902, described these cells as *glandes interstitielles de l'ovaire.*

Biedl (39) says, "that the secondary female sex characteristics, especially those of the genital tract, are dependent upon the interstitial cells of the ovary is at present not proved." He further directs attention to the fact that the x ray destroys the Graafian follicles alone. The interstitial tissue is not only preserved, but it hypertrophies.

While the observations thus far made upon the ovary and its secretions are not as conclusive as in the case of the male gland, Biedl states, "that the tissue which performs the function of external secretion is also the site of production of the ovarian nonsexual hormone, which exercises an alterative influence upon a large number of tissues and functions, is suggested by analogy with the male sexual gland."

This is distinctly contradictory to Biedl's attitude regarding the testis, and his reasoning by analogy seems obscure. In any event, differences of opinion as to the precise histophysiological source of the internal secretion of either the ovary or the testis have little bearing upon the experimental or therapeutic value of implantation of the sex gland tissues in their totality.

The real, probable, or possible results of implantation of the ovary depend—so far as the properties of the gland *per se* are concerned—upon, first, the existence, effects, and continued production of an internal secretion; second, the existence, effects, and continued production of the ordinary generative sexual secretion; third, successful implantation of a normal gland, in whole or in part, with its structure entire; fourth, permanent growth of the implanted gland.[3]

Granting that the Graafian follicle, the corpus luteum, and the ovarian interstitial tissue are equally important, or that only one of these tissues really is important from the internal secretory standpoint, the procedures and results should be the same, unless it is held that a complexity of origin impairs the effects of the gland secretion, which obviously it cannot. The first work of any importance in ovarian transplantation from the living was done by Robert T. Morris, of New York.

From Leo Loeb's pioneer experiments in cultivating tissues *in vivo* and *in vitro,* some years prior to Carrel's recent remarkable experiments, I had suspected that more or less successful grafting of the human testis from one living subject to another was possible. Aside from the recorded experiments on animals, this was suggested to my mind by observation of the effects of division of the spermatic cord, exclusive of the vas deferens, in a large number of varicocele operations, and experimental severance of the cord, including the vas, in numerous hernia operations on old men in a certain public institution. In these cases I closed the hernial opening over the "tucked up" proximal end of the cord, and sutured the distal end of the cord across the ring. In respect to division of the cord, the procedure was similar to the operation for hernia later suggested by Blood-

[1] In reference to this point, Waldstein and Ekler's experiments (Der Nachweis resorbirten Spermas im weiblichen Organismus; abstract in *Deutsche medizinische Wochenschrift,* October 9, 1913) are very interesting. They found that within two and one half to sixteen hours after coitus, the blood of the human female contained a ferment which peptonized the albumin of testicular extract. Comparing this with Fauser's observations in dementia præcox, we are justified in suspecting that the internal secretion of the testis is in part eliminated by the semen. The marked improvement so often noted in the nutrition of sterilized—not castrated—males, and resulting from continence, thus may be scientifically explained. It is possible, however, that there is a change in the ovarian hormone itself, under the stimulus of coitus. The sense of well being experienced after normal coitus by both sexes probably is due to a large dose of hormone entering the circulation on the one hand from the testis and on the other from the ovary.

[2] Apropos of the nutritive stimulant action, one of my own experiments is interesting. Implantation of testes from a year old cock upon a nonrelated capon of the same age resulted in an improvement in carriage, increased glossiness of plumage, a better appearance of the face, comb, and wattles, increased liveliness, and a disposition to combativeness, with a slight development of sex activity, which last phenomenon was of short duration.

[3] Stich, *Deutsche medizinische Wochenschrift,* September 25, 1913, in a résumé of the present status of organ transplantation, sums up the subject of ovarian transplantation by stating that it occasionally succeeds in animals which are blood kin. Stich altogether ignores testicular transplantation, apparently as a subject on which no data are available.

good. I early found in operating for varicocele that, unless infection occurred, complete division of the cord was not followed by atrophy of the testis, even when the operation involved complete extrusion of the gland via the operation incision. Apparently the circulation of the cord could not be restored at the point of junction of the ends of the divided portion, before the testis died of innutrition, if the salvation of the gland depended upon the spermatic artery and the artery of the vas.

The vascular supply of the tunica vaginalis alone apparently being of no magnitude, the notion obtruded itself upon me that possibly comparatively little blood was really necessary to the life of the testis, and, further, that the juices of the surrounding tissues might be sufficient to preserve the life of the organ or at least a portion of it. Reasoning by analogy, the implantations of ovarian tissue subsequently performed by various operators, in which gland tissue from the living was replanted in the living, seemed quite conclusive evidence of the possibility of successful testicle grafts under similar conditions.

With the publication of Carrel's remarkable experiments, and having in mind not only numerous experiments with tissue from the living published in the literature and recent developments in the study of internal secretions, but certain preconceived ideas of my own, I became convinced that implantation upon living subjects of sex glands from the dead body was both practicable and likely to be therapeutically successful. I felt also that if successful, the procedure possibly might open up avenues of medical and surgical therapy which would be somewhat staggering, even to those of us who are not easy to astonish.

During the past year or more, I have been endeavoring to secure opportunities for experimentation with material from the dead body in sex gland implantation in both sexes. That the difficulties attending my efforts were great, should be obvious to any one who knows the prevailing sentiment in America against using the dead for scientific purposes—especially the recently dead. These difficulties were greatly enhanced by the fact that it seemed desirable to secure glands from special subjects, of a certain age, dead of violence, in fresh condition, and as certainly free from syphilis as it was practicable to determine. The Wassermann test might, or might not be practicable. Having secured the proper cadaveric material for experimentation, it still remained to secure a living subject who would permit the experiment.

With the double object of experimental sex gland implantation and of testing the procedure in the treatment of dementia præcox, I attempted to secure a favorable subject afflicted with this disease, and endeavored to enlist the cooperation of several medical friends whose opportunities for securing material were better than mine, but without success. The double problem of securing human sex glands under proper conditions and of having a complaisant subject ready and waiting for the experiment seemed insoluble, until I thought of the plan of combining surgeon and subject and resolved to perform the experiment upon my own person.[4]

January 16, 1914, there were placed at my disposal two appropriate male subjects from which to select the material necessary for gland implantation. One of these showed a lesion on the penis, probably of a nonsyphilitic, suppurative character—seemingly a periurethral abscess—and was consequently rejected. The other, a suicide by gunshot, and a relatively inferior but apparently healthy subject, eighteen years of age, was selected. The subject had been dead seventeen hours, having lain at the undertaker's under the ordinary conditions and temperature since shortly after death. The weather at the time was very mild. In my haste to secure the necessary material, the appliances necessary for the Wassermann test were forgotten, hence I was compelled to rely upon such history of the subject as was obtainable and a careful examination of the body, especially of the genitals, including incision and macroscopic examination of the lymphatics. The danger of syphilis obviously could not be entirely eliminated, but was not sufficient to weigh heavily in the balance of opportunity to secure the long sought material.

Both testes were removed as aseptically as practicable, the instruments and gloves being sterile, and iodine being freely employed in lieu of the customary scrubbing. The testes immediately were placed in a jar of sterile normal salt solution.

Case I. *Autoimplantation of the testis; subject fifty-six years of age.* Seven hours after securing the necessary material, and twenty-four hours after the death of the subject from which it was removed, I implanted in my right scrotal sac one of the experimental testes. The operation was performed in my office, with the assistance of my former associate, Dr. Carl Michel, whose loyalty and intelligent cooperation throughout my experiments cannot be too highly commended. The conditions, so far as asepsis was concerned, obviously were not those of an up to date operating room, with the usual corps of nurses, but were as satisfactory as was possible under the circumstances.

Technic: Local anesthesia was employed—a ten per cent. solution of novocaine in one per cent. urea and quinine hydrochloride. Of this I injected about a dram and a half. The anesthesia was satisfactory so far as the skin was concerned, but by no means so as regards the deeper tissues, merely because I took especial care not to puncture the veins of the cord and also to avoid infiltration of the tissues about the cord at the site selected for the implantation.

I made an incision two inches in length, in the midscrotal region, about an inch external to the right of the scrotal rhaphé, and dissected down to the cord. The awkward position necessary to the work and the distance of the field from the operator's eye were such that I inadvertently cut into the tunica vaginalis. The escape of vaginal fluid and the appearance of the testicle at the bottom of the wound gave the first intimation of the accident. I requested Doctor Michel to close with a pursestring

[4]Lespinasse, in his paper herein quoted, speaks of being surprised by the ease with which material is obtained from living subjects. The author has not noted similar "ease" in securing testes. Incidentally, it is well to remember certain legal responsibilities involved in taking material from the living, even when freely tendered, save in very exceptional instances. As Lespinasse's first case of transplantation of slices of testicle was done in January, 1911, and he has just published his first case for the second time, with a single additional case (*Chicago Medical Record*, July, 1914), it is safe to infer that material is not so abundant as he thought at first. In passing, I note with some curiosity that in his more recent paper, he has not mentioned the first two cases of sex gland implantation reported in my present paper, although they were reported some months since in the *Bulletin* of the Chicago Medical Society, and thereafter were extensively quoted. In scientific work it is desirable in all fairness to make references as complete as possible. In connection herewith it is worthy of comment that of the fifteen references given by Lespinasse in his reprint, seven are inaccurate.

suture of very fine catgut the opening in the tunica vaginalis, and proceeded with the operation.

I next made beneath the deep fascia a pocket about two inches in depth, at the bottom of which was the cord. Into this pocket, directly upon the cord, I implanted the testis, already prepared by removal of the epididymis and decortication to the extent of about half its surface. The fascia was closed with a purscstring suture of fine catgut, following which, bismuth subiodide and the usual gauze dressing were applied and a suspensory was adjusted.

Postoperative course: Probably because of undue movement, the exigencies of my practice at the time making it impracticable for me to rest physically, there was a little superficial hemorrhage, forming a small clot immediately beneath the skin incision. Saprophytic infection occurred, with considerable edema of the penis and scrotum, extending well up toward the inguinal ring. On the fourth day I opened the superficial portion of the wound, drained, and asepticized it. There was not then nor subsequently any pus infection during the progress of healing. There was a little over 1° F. rise in temperature, lasting four or five days.

There was considerable pain, following undue motion, on the eighth day after the operation, and a small quantity of seminiferous tubules protruded from the wound, the pursestring fascial suture evidently having given way Although there was no rise in temperature and, as already stated, no pus infection, I now concluded that the experiment was a failure, and decided to remove what apparently was a somewhat dangerous foreign body. I therefore requested Doctor Michel to remove the implanted gland, and as there was a little resistance when traction was made on the protruding gland tissue at the bottom of the skin (i. e., the extrafascial wound), he attempted to remove it entire by forcible traction. The resistance to traction and the pain attending this procedure demonstrated pretty conclusively that it would have been wiser to let the gland remain.

The gland splitting longitudinally, only half of it, and, strange to say, the more solid portion, covered by the tunica albuginea, came away. This, on examination, showed well formed and abundant vascular adhesions, which apparently conclusively showed that the implantation was a success. I therefore resolved to leave the decorticated remaining half of the gland *in situ*. At the time of the implantation the semidecorticated gland was so soft and so readily became extruded, that it was with difficulty retained in the implantation cavity while the pursestring suture was being inserted and tied. Had I remembered this circumstance, the mere fact that a moderate amount of traction, or even slight pressure, was not sufficient to dislodge the implanted tissue from its bed and extrude it, would have suggested the wisdom of allowing the gland to remain.

After the removal of the portion of gland there was some increase in the local inflammatory symptoms, due to simple trauma. This, however, subsided within forty-eight hours. Immediately following the removal of the gland tissue, there was a moderate discharge of a mucosanious looking secretion, which continued in gradually diminishing quantity for five weeks, at which time the sinus was completely healed. The tardiness of healing in a noninfected wound is worthy of note, suggesting the characteristics of fistulæ of glands in other regions, notably the parotid.

Numerous microscopic examinations by Doctor Michel of the fluid from the fistula showed blood corpuscles, leucocytes, and immature spermatozoids, such as normally are found in the testis prior to their complete elaboration in the epididymis. There was no evidence of pus infection, the fluid being free from pus cocci.

After the extraction of the portion of the gland, there was no further appearance of seminiferous tubuli in the wound, neither was there any débris nor broken down gland tissue in the secretion from the "fistula." After the inflammation in the surrounding tissues had completely subsided, a distinctly circumscribed, ovoid, insensitive body adherent to the spermatic cord could be distinctly felt. This mass measured approximately 4.5 cm. by 3 cm. by 2 cm., and was evidently composed of the remaining portion of the testicular gland structure, with a certain amount of new connective tissue investment.

Throughout the progress of healing there was considerable neuralgia of the traumatized cord and testis and moderate pain and sensitiveness in the opposite testis. Later the pain gradually disappeared.

The result has been inspected and verified by a number of my professional friends.

The size of the mass has gradually decreased. June 1, 1914, it was a smooth, fairly movable, ovoid, insensitive, circumscribed, typically glandular body, about the size of a small almond, still loosely attached to the spermatic cord. At present writing, August 1, 1914, the mass is nearly round, about the size of a hazel nut and, strange to say, slightly sensitive. It has not diminished much if any in size for several weeks, although I have expected still further shrinkage. I have noted that it varies considerably in size at different times. This is very suggestive of actual function.[5]

(*To be continued.*)

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## HETEROPLASTIC GRAFTING OF TESTICLE.

By Robert Tuttle Morris, M. D.,
New York.

A letter received from my friend Dr. G. Frank Lydston stating that he is publishing a communication relating to the subject of the grafting of testicle, prompts me to cite a similar case and to send some letters bearing thereon.

Case. W. A. S., aged forty-nine years, was referred to me by Dr. W. J. M., of Rochester, Minnesota. Ten years previously, as a result of being thrown by a bucking horse upon the pommel of a Mexican saddle, both of the patient's testicles had been crushed and had been subsequently removed by operation. Shortly afterward, all characteristic masculine cenesthesia was lost and the patient, a large strong man, became extremely nervous with periods of great depression, shedding tears at slight provocation. As a man of education and intelligence he comprehended the entire situation and knew the reason for his psychic condition, although he said that it was at times unbearable.

On consultation with the patient I recalled to him our experience with ovarian grafting. After I had published the description of ovarian grafting in 1895 and had introduced the idea, a large number of authors soon furnished data of their own bearing upon the subject. There was a general conclusion along lines which biologists might have anticipated, to the effect that the tissues of one individual are antagonistic to the tissues of another individual. Therefore, heteroplastic grafts of any sort are commonly absorbed promptly by the host. The degree of antagonism between individuals varies greatly, and occasionally we may find two people (or other animals) which receive each other's tissues with good grace, if a bit of levity may be pardoned.

The patient, W. A. S., was willing to take the chances of obtaining benefit from a grafted testicle, and entered the Post-Graduate Hospital, February 4, 1914. The first patient who offered opportunity for furnishing the graft had undescended testicle and hernia; he agreed to allow me to use a part of his testicle for grafting purposes. This patient, a young man twenty-six years of age, responded so strongly, however, to the von Pirquet test for tuberculosis that I preferred not to make use of his tissues. The next case was one of a man fifty-six years of age with a very large hernia, who made no response to the von Pirquet test for tuberculosis nor to the Wassermann test for syphilis and who gave a record of good general health.

A wedge of tissue was taken from the testicle of this patient and placed in normal saline solution until W. A. S. could be anesthetized and prepared. The segment of testicle was cut into four slices with a sharp razor, these slices averaging about three mm. in thickness, and in length approximately that of the testicle from which they had been removed. One of these segments was engrafted in the right scrotum of W. A. S., another one was placed beneath the fascial sheath of the right rectus abdominis; and the third segment placed beneath the sheath of the left rectus

[5] That the mass is now largely composed of hormone producing tissue the author is firmly convinced.

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## Original Communications.

### MUSCLE BOUND FEET.


BY RUSSELL A. HIBBS, M. D.,
New York.


Systematic walking is perhaps the form of exercise most beneficial to health, and certainly it is the one available to the greatest number of people of all ages. It is a fact, however, that many people, both young and old, are disinclined to walk, although they have been urged to do so by their physician and fully appreciate its value to health. It becomes of practical importance, therefore, to inquire into the causes of this disinclination.

Among the many causes there is one that occurs very frequently and has received too little attention, namely that of muscle bound feet. A muscle bound foot is primarily one in which dorsal flexion at the ankle joint is limited to an angle of ninety degrees or more, by a short calf muscle. To order a patient with this condition to walk a given distance each day, and on his failing to do so, as is generally the case, to consider him lazy and indifferent, is as unreasonable as it would be to consider a person with a muscular defect of the eyes unintelligent, because he did not read a certain amount each day.

Walking cannot be healthful unless it is performed normally and this is possible, other things being equal, only when the feet are normal in structure and are held in relation to the leg so that weight is properly distributed by the control of muscles normally balanced, contracting through normal arcs, in response to impulses originating in the central nervous system.

Dorsal flexion of the foot at the ankle joint should be to an angle of eighty or seventy degrees to the leg. This allows for the free swing of the tibia forward over the articular surface of the astragalus to the limit established by the change of the centre of gravity. This causes the distribution of the weight through the foot in a constantly changing direction, makes possible the proper rest periods of the calf muscle, and insures the proper action and development of the opposing muscles and of the intrinsic muscles of the foot.

When dorsal flexion is limited by a short calf to an angle of ninety degrees or more, the stride is shortened, the contraction of the calf is more frequent, and its rest periods are shortened. Or else, if the stride is not shortened, when the tibia reaches the limit of its swing forward over the articular surface of the astragalus established by the short calf, tension is made upon the muscle and it contracts, elevating the heel. The muscle is held in a state of contraction for a longer period of time, and it also suffers somewhat from tension made upon it. Its contraction is made in response to that tension, rather than to an impulse originating in the central nervous system, excited by a change in the centre of gravity. The heel, being held elevated for so long a period, with the weight borne upon the distal ends of the metatarsal bones, adds the important element of foot strain.

While the primary defect of such a foot is a short calf muscle limiting dorsal flexion, the consequences of this condition, when existing for any considerable length of time, are other changes in the foot and also impairment of the nervous system.

The opposing muscles are weak, because the amount of work they do is measured by the degree of dorsal flexion, and this being limited, their development is impaired. This fact may be demonstrated in every case.

The weight bearing structures, intrinsic muscles, ligaments, and bones are affected, because the weight is not properly distributed in the foot through a centre of gravity which is constantly changing. With the swing forward of the tibia over the articular surface of the astragalus checked by the short calf, this cannot take place. Evidence of this is seen in the appearance of changes in relation of the foot to the leg, such as abduction, changes in relation of the tarsal bones to each other, impairment of arch, changes in relation of the metatarsal and phalangeal bones causing hammertoe and Morton's toe, the appearance of callosities over the distal ends of the metatarsal bones, and pain in the foot.

The circulation of the blood in the foot and leg is affected, because its perfect accomplishment depends to a very important degree upon normal freedom of the muscle action. Evidence of this disturbance is shown by a cold and clammy condition of the skin, excessive perspiration, feelings of heaviness and numbness, and a slight varicose condition of the veins of the calf. In many cases of flat foot, about which so much has been written, this muscle abnormality existed long before the appearance of the deformity and was an important factor in its cause.

The gait produced by feet in such a condition must of necessity have an unfavorable effect upon the nervous system, because there is an overproduction of those waste products of muscle action which cause fatigue and muscle tension and affect the nerve ends in the fibres of the calf muscles by the impairment of the circulation, and so give rise to foot strain. Evidence of this is given in the fact that all these patients suffer from excessive fatigue,

# IMPLANTATION OF THE GENERATIVE GLANDS AND ITS THERAPEUTIC POSSIBILITIES.*

*Successful Autoimplantation of a Testis from a Subject Dead Twenty-four Hours. Other Successful Implantations of Testes and Ovaries from Dead Subjects. Experimental Implantations in Various Conditions, and Cross Implantations of Testes and Ovaries Taken from Dead Subjects.*

By G. Frank Lydston, M. D.,
Chicago,
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(*Continued from page 753.*)

## APPARENT LOCAL RESULTS OF THE EXPERIMENTAL AUTOIMPLANTATION.

That this mass was for many weeks composed of living, functioning testicular tissue is, to my mind, not an open question. Dead tissue of such loose structure and soft consistence as are the tubuli seminiferi, devoid of the normal fibrous envelopment—the tunica albuginea—and connected by an open wound with the surface of the skin, could not logically be expected to remain *in situ,* much less to become encysted by connective tissue, but would have broken down and come away, either in mass or as débris. Nor would the sinus have healed so long as necrotic tissue was present at its tissue terminus. If the mass was purely inflammatory, it should not have become circumscribed, freely movable on its cord attachment, and relatively lasting, but should have disappeared *pari passu* with the absorption of exudate in the surrounding inflammatory area. The persistence of the tissue mass at the site of implantation, together with the continuance of the apparent physiological results, appear to be conclusive, an opinion which has been held by all who have noted the progress of the case.

As to whether the implanted tissue will eventually be entirely destroyed and replaced by connective tissue is an open question. I venture the opinion that it will not. If the implanted tissue finally should disappear, the temporary nature of the implantation result might logically be explained by faulty technic, embracing too free decortication, which, as elsewhere stated, in future can be avoided. The testis and ovary, if not completely decorticated, should be more likely to endure permanently after implantation, even though considerable atrophy occurs. In this respect they probably differ from the thyroid and other glandular tissues.

If trophic nerve supply is essential to structural integrity, then more or less atrophy of implanted gland tissue should be expected, whatever technic is employed, unless it is conceded that regeneration of such nerve supply may occur.

That apparently complete destruction of the generative portion of gland tissue would necessarily nullify the physiological effects of the implantation is by no means certain. With hardly perceptible tumor, the Leydig cells might still remain and function, producing the all important hormone. They seemingly proliferate and may increase, in amount and activity, the production of internal secretion. On the other hand, they might eventually be so changed by blood, tissue, and trophic influences as to become inert, as regards their internal secretory activity.[6]

In brief, whether or not there is eventually apparent disappearance of the gland tissue after a successful implantation, the method theoretically should be therapeutically useful and its benefits permanent: First, because the interstitial gland tissue may remain and function, producing hormone; second, because the hormone may have done its work of regeneration, the conditions for which we operated having been so profoundly modified by nutritional changes that they do not recur, with consequently no indication for continuing the remedy. If complete atrophy eventually is the fate of implanted testes and ovaries, irrespective of whether the entire gland or pieces are used, and sufficient benefit has not resulted, we still may have recourse to successive implantations of fragments of glands, repeating the "treatment" as often as may seem necessary.[7]

## SUGGESTIONS FOR IMPROVEMENTS IN TECHNIC.

The difficulties under which I labored in my autoexperiment require no further comment. That not only the sex gland implantation, but also the technic of the process was necessarily experimental is self evident. In my future work the procedure will be modified by leaving intact all the tunica propria of the testis, save from two to four narrow, longitudinal surfaces, about two or three mm. in breadth, running the entire length of the gland. These narrow bands of decortication will provide for nutrition by the tissue juices of the implantation bed during the formation of vascular adhesions and new blood supply. Vascular adhesions naturally may be expected to form at the points of decortication. The limited area of decortication will not subsequently permit of an invasion of connective tissue from the surrounding structures sufficient to endanger the delicate glandular elements of the implanted organ. The portion of the tunica albuginea still remaining will afford ample protection for the gland tissues beneath it, and probably will soon regenerate and cover such portions of the decorticated area as are not occupied by new bloodvessels.

Incidentally, the tunica albuginea of the testis and ovary probably plays an important part in the trophic or nutritive selective function of the gland, and possibly in the formation of hormone. Thus if the tunic alone remains and the gland tissue proper atrophies, all may not be lost, so far as permanent therapeutic results are concerned.

Under favorable conditions, local anesthesia is sufficient for implantation operations. In the in-

[6]Fresh triturations of gland tissue even may be used in the form of an emulsion, injecting the fluid almost anywhere beneath the skin. Excepting implantation, this would seem to be the most rational method of administering hormone.

[7]The danger of the phenomena characteristic of anaphylaxis naturally suggests itself in connection with successive implantations and testicular emulsion treatment. The author has implanted the testes of cocks repeatedly in the same subject, and even in female fowls without evil results. Implantation in fowls is a severe test of protein dosing. If the testis of the human being was as large in proportion to the body as that of a lusty cock, the gland would weigh several pounds; this aside from the relatively greater activity of the glands of the fowl. The author has also experimented upon guineapigs, upon himself and upon a number of other human subjects with large doses of human brain emulsion, given beneath the skin and intramuscularly, without injury.

sane, general anesthesia is likely to be required, and I have thus far employed it. Asepsis should be most rigid both in securing the glands and their implantation. I am now removing them from the dead body without permitting my hands to come in contact with them. The glands should be removed from the body as soon as possible after death. The slightest degree of decomposition will insure failure. Obviously haste in removing the glands is not so urgently necessary in cold as in warm weather, nor is it so necessary immediately to implant the glands.

The glands should be placed in sterile normal salt solution, or, preferably, in Ringer's solution, immediately on removal from the body, and under favorable conditions implanted within twenty-four hours. As Carrel has shown, tissues may be kept frozen for several weeks and still retain their vitality. This fact perhaps in future can be taken advantage of in preserving sex glands for implantation. In one of my cases (Case IV) the ovary was kept in a refrigerator for a week. In all the cases which followed it, refrigeration was employed for from two to five days, but the results were not encouraging.

An aseptically prepared gland, when frozen, can undergo no change save a certain degree of "autolysis" which will prevent its functioning. Even complete autolysis would not make dangerous the implantation of an aseptic gland. The autolyzed tissue would be likely to be merely appropriated as nutriment by the living tissues of the implantation bed. It is worthy of note in connection herewith that my former associate, Dr. Carl Michel, has experimentally demonstrated that gland tissue kept at a temperature of 37° C. for about twelve hours, loses its functional activities—"functional autolysis." This, he states, is due to relative overfunctioning in the absence of nutriment. Other forms of autolysis he terms: (a) physical; (b) putrefactive.

The loss of activity of the gland in "functional" autolysis is probably due, not so much to a lack of nutriment as to biochemical products of the gland tissue itself, these products (both internal and external secretion) being inhibitory to the vitality of the tissues which produce them. This involves a familiar principle in biology, particularly in pathogenic germ biology.

Excreted into and modified by the blood after implantation, before autolysis has occurred, the gland products (secretion) returning to the gland, are stimulant to its function and nutritive to its cells.

Doctor Michel suggested that tissues designed for implantation should be kept in Ringer's solution at a temperature not below 0° C., and not longer than two weeks, the object being merely to inhibit the biochemical function of the cell enzymes without destroying either them or the cells that produce the ferment.

Doctor Michel is probably correct in his conclusions, although he has overlooked a most important point in his reasoning, viz., freezing possibly may destroy the delicate cells of Leydig and the ovarian interstitial cells of Bouin, without necessarily destroying the rest of the gland. Thus it is not improbable that glands which have been frozen may sometimes apparently survive implantation and yet not function, especially from the internal secretory standpoint. The aim of implantation is not to insert what must inevitably become a functionless mass of connective tissue and useless generative gland cells into the body of the recipient. The failure of the implantation of glands which were merely "refrigerated" while suggestive, of course does not prove that glands which are completely frozen may not be successfully used.

I am still inclined to believe that the epididymis should be removed where the object is merely gland implantation for experimental or for therapeutic purposes to secure the benefits of internal secretion. While the epididymis probably produces hormone, it is here of no particular service, and by its mere bulk and the mechanical irritation it produces, greatly enhances the danger of failure of the implantation. Again, the removal of the epididymis affords a surface favorable to adhesion and nutrition, without extensive decortication and exposure of the delicate tubuli seminiferi.

The results of anastomosis of the implanted testicle thus far have not been very encouraging. Very little work, however, has been done in this direction on the human subject, and it seems to be a legitimate field for experimentation. Anastomosis of testes from closely related subjects—especially from the living to the living—at least is hopeful, despite the great difficulties attending anastomosis of the spermatic vessels.

When, for any reason, it is desirable to attempt to preserve the generative sex function of the implanted gland, the epididymis and a portion of the vas may be preserved for anastomosis, a procedure which, mechanically at least, is perfectly feasible—and successful in simple anastomosis of the duct in the living subject—by a method devised by myself. This consists of coupling the severed ends of the vas by a strand of heavy silkworm gut introduced into the lumen of the distal portion of the tube and passed down to the epididymis, the other end of the gut being passed well up into the proximal end of the vas and through its wall, and made to emerge through a puncture in the skin above the upper angle of the operation incision. The ends of the vas are brought together on the gut coupling or splint, and covered with the fascia of the cord, much as a plumber wipes a joint. The wound in the scrotum is now closed with fine catgut or horsehair sutures. On the tenth day, the strand of silkworm gut is withdrawn. This method of anastomosis can be applied without disturbing the cord or testis of the recipient of the implanted gland, further than to expose and divide the vas deferens for anastomosis, as shown by an experimental case of my own.

The obstacles to anastomosis of the small vessels of the cord appear to me to be at present insuperable. That more or less successful anastomosis of a testicle immediately after its removal from the living body is practicable in a certain proportion of cases, is probable. The importance of this is easy of comprehension. There are countries where there are no legal obstacles to persons disposing of portions of their bodies as they see fit. Possibly our

own laws may one day be amended so as to enable us safely to use gland material from the living that is voluntarily submitted to us by its possessor. Meanwhile, if, as is possible, anastomosis of testes taken from dead bodies should prove to be even moderately successful, some wonderful work is likely to be accomplished.[8]

That the chances of failure of implantation are greater where anastomosis is performed goes without the saying, as experiments have not been encouraging and relatively free incision and exposure of the site of operation is necessary, and more tissue of a lesser degree of vitality is implanted than where our object is merely to secure the benefits of internal secretion. If, however, the gland itself should survive, the anastomosis is not likely to fail. Here again arises the question whether Carrel's results in kidney transplantation in the lower animals are equally important as bearing upon sex gland transplantation in human beings.[9] Obviously, rest in bed for some days should be enjoined in implantations, and for a more prolonged period when anastomosis is performed.

The site selected for implantation is an important consideration, and should be decided on the merits of the individual case. It may be that the sex glands will finally be shown to be quite as successfully implanted in one part of the body as another, but at present writing I venture to suggest that there are points of election. In the male, the site should preferably be the neighborhood of the testis and spermatic cord. The tunica vaginalis will invest the implanted gland on one side, and thereby give it in part a natural covering. The gland tissue probably will adhere more readily to the tunica vaginalis than to the other tissues, and there will be very little connective tissue at the point of adhesion, subsequently by its contraction to menace the integrity of the implanted gland. Future experience may show the advisability of folding and stitching the tunica over the gland. This probably would be wise where only a portion of testis is implanted. I would suggest, also, that where only a portion of the gland—this also applies to the ovary—is implanted, the cut edges of the tunica albuginea should be sutured together to protect the delicate gland tissue from connective tissue invasion. Whether or not there is a special "selective" trophic or blood nutritive element in the environment afforded the implanted tissue by the proximity of its bed to the testicle, is an open question.

Future experience may change my view, but at present it seems doubtful if it would be wise to implant the gland into the cavity of the tunica vaginalis. The resulting mechanical irritation, conjoined with trauma of the sac, might produce so much exudation and swelling as to cause severe pain and even endanger the recipient's own testicle. Aseptic extravaginal implantation in no way endangers the subject's testicle.

The second best implantation site doubtless is the pelvic properitoneal space, as will later be suggested for the ovary.

As third choice of location I suggest the mons veneris, the pubis being shaved and the incision made transversely just below the upper margin of the pubic hair. The length of incision, of course, will vary with the amount of fat, an incision one inch in length being ample in spare subjects. By the downward insertion and opening of a pair of forceps or blunt scissors, a pocket may by dry dissection easily be made for the gland. This pocket should extend downward to just above the pubic symphysis. In this location, after the hair again has covered the part, neither the scar nor the small tumor which will result—if the implantation is successful—will cause comment by others. The cavity of Retzius is also safe and accessible. The gland should be implanted high up, or well over to one side to insure peritoneal contact. The axilla appears to be another eligible location, the incision being made well away from the centre of the axilla and the bottom of the pocket made to correspond with about the centre.

One important difference between male and female must here be noted. The former is normally dominated by the psychic influence of a testis that can be seen and felt. He is always conscious of its presence. The reverse is true of the female and the ovary. The psychic benefit of the consciousness of a demonstrable testis, especially in the scrotum, must not be forgotten in the case of the male. It will be by no means a negligible quantity in external ovarian implantations in the female. As to what extent exposure to traumatism may militate against the success of implantations in exposed sites is a matter for future determination. It is, however, worthy of consideration.

In ovarian implantation of glands from the dead subject, which is quite as practicable as similar testicular implantation, and for which the necessary glands of proper quality are much easier to secure, the order of choice of sites for operation appears to me to be as follows:

1. The properitoneal space.
2. The cul-de-sac of Douglas (extraperitoneally).
3. The labium majus, the incision being made high up and the part "pocketed" downward, as in the case of the scrotum.
4. Beneath the mammary gland.
5. The pubic region, as in testicular implantation in the male, better, perhaps, the cavity of Retzius where observation of the implanted tissue is not desired.
6. The rectus muscle.

The peritoneum forms the normal environment for the ovary, and if half or more of the surface of the implanted organ is made to rest permanently on the peritoneum—which by adhesion in successful cases will form a protective and nutritive invest-

[8] It should be remembered that "considerable atrophy" of the testis may occur, without either the generative or the hormone producing function of the gland remnant being necessarily destroyed.

[9] The author feels that he cannot too often insist that failure in transplantation of an excretory organ has little bearing on that of a double secretory organ like the testicle or ovary. Doctor Carrel seems to believe that the results of his experiments should estop organ transplantation altogether, judging by his recent paper before the American Surgical Association. He apparently loses sight of the hormone therapy angle of organ transplantation. I regret that he did not discuss this, more especially as I had corresponded with him about my own experiments, several weeks before. To have mentioned my experiment perhaps would have been only fair to the general scientific bearings of organ transplantation. I further insist that while the preservation of the generative function of the transplanted ovary is not to be expected—save possibly in testicle anastomosis under the most favorable conditions—and that of the testis possibly not at all, sex gland implantation still offers great therapeutic possibilities. As to the local possibilities, I would refer in this connection to the remarkable results obtained in Case VI of my series.

ment for the gland—the chances for success will be greatly increased.

An eligible point is the ilioinguinal region, well out toward the anterior superior spine of the ilium. After exposure of the peritoneum, a pocket should be made anteriorly to it, downward into the pelvis.

The cul-de-sac of Douglas is an available and logical site for implantation. A small vaginal incision should be made posterior to the uterus, the peritoneum being carefully pushed up with the finger, thus making a pocket for the reception of the implantation gland.

The labium majus is a particularly eligible site, because of the proximity of the canal of Nuck, which is a peritoneal derivative and the analogue of the tunica vaginalis in the male.

I will reiterate that a point in favor of "exposed" sites of implantation in some cases is the psychic effect of objective evidences of success on the mind of the patient, which sometimes is so desirable. Incidentally, the surgeon can determine whether or not the implantation is successful.

The methods of Tuffier and of Martin of implantation within the pelvis and rectus muscle of ovarian tissue from living donors, is a procedure entirely different from that under discussion. Heterointraperitoneal implantation within the pelvis is unnecessary and has an element of danger. For experimental purposes especially, it is usually best to implant the gland in a part accessible to observation, and from which, if desired, it can be subsequently removed. To imitate the natural environment as closely as possible, I suggest the experiment of partially wrapping the testis in a graft from the tunica vaginalis or peritoneum, and the ovary in "appendage" peritoneum, whenever the implantation site is more or less remote from the normal ovarian or testicular environment; in brief, where the environment would otherwise be alien, or possibly even hostile, it can possibly be made temporarily akin, or at least friendly. Should the membranous lining of the implantation pocket, as is probable, be absorbed, it will have served its purpose of a matrix for the growth of a thin protective layer of connective tissue. I suggest a similar technic in thyroid implantations, also that implantation in the normal habitat of the thyroid is more logical than elsewhere. Where the tissue has no capsule, or the capsule is insufficient, fascia may be used as a protective "capsule"; theoretically, a piece of peritoneum should be ideal.

Ordinary connective tissue is a deadly foe of glandular, brain, and nerve tissue, as shown by its effects in cirrhosis of the liver, interstitial nephritis, and various diseases of the cerebrospinal axis. So far as possible, therefore, we should protect the implanted gland from invasion by it. It is well to remember that the environment of the ovary is such that it should be removed from the dead body relatively earlier than the testicle. The close proximity of the bowel is favorable to early pelvic decomposition.

In implantation in either sex, care should be taken: First, to make as limited an incision as is compatible with the insertion of the gland. As the gland is soft, and the skin and fascia elastic, a very small incision will suffice. Second, to insure that the dissection of the pocket shall be as dry as practicable and to traumatize the tissues as little as possible. Third, to avoid injuring the delicate gland tissue during its preparation and implantation. It should not be regarded as dead insensitive tissue that may be recklessly mauled, but as living tissue to be carefully handled. Fourth, to use the finest chromic gut—or better, perhaps, iodinized gut—and insert no more sutures than are actually necessary to a perfect closure. The pursestring suture for the fascia is ideal. Fifth, at all times to avoid rough manipulation of the implanted gland during healing, and especially to manipulate it as infrequently and as gently as possible, while adhesions and vascular supply are forming.

The problem of the quantity of gland necessary for implantation is a most important one. If the major premises outlined—or suggested—in this paper are correct, this problem practically involves the question of the proper dose of internal sex gland secretion in various conditions and in individual cases. If a fair average of successes should prove to be practicable, an entire testicle body is preferable. In general, however, probably one half of a testis is sufficient to give definite physiological results, and is surer to be preserved than a whole gland. In the case of the ovary, however, I am inclined to believe it better to implant an entire ovary, even though a small portion of the gland is seemingly sufficient to preserve the secondary sex characteristics and often even to prevent the nervous wreckage incidental to oophorectomy.

If the implantation is successful, the dose of internal secretion, however large or small it may be, is continuous. It is for this reason that a relatively small portion of implanted sex gland tissue is likely to be efficacious. Even though implantation should prove successful, definite results should probably not be hoped for before six or eight weeks after the implantation, at which time establishment of circulation in the gland—if it survives—may reasonably be expected.[10] In general, it is probable that such results as may occur will be noted earlier in testis than in ovary implantation, and in the case of the testis, earlier where the gland has been decorticated, although complete decortication endangers permanent success. The establishment of a sufficient vascular supply is essential, not only to the life of the gland, but to the necessary supply of materials from the blood for the elaboration of internal secretion, and to the entrance of the latter into the blood.

The story of sex gland internal secretion therapy can be simply told. *The hormone is a cell stimulant, nutrient, and regenerator.* The application of the principle is, of physiological necessity, far reaching. It may in a measure serve to reconcile Bichat's humoral pathology and the cellular pathology of Virchow and prove them to be equally logical, but only half truths. A more highly developed neuropathology will probably be the connecting link between them. The germ, however, will not grow less important in etiology, but, as time goes on, undoubtedly will be aggrandized as a causal factor of disease. In brief, the microorganism will be more clearly understood as merely the agency through

[10] From the results of my own experimental work I infer that results may be expected at a much earlier period.

which most pathological machinery is set in motion.

Should implantation ever become an established therapeutic procedure, as it seems logical to predict that it will be, it will doubtless be found that the required dose of internal sex gland secretion will be governed by: 1. The age and general bodily vigor of the recipient of the gland. 2. The age and presumed general and sexual vigor of the dead subject from which the gland was taken. 3. The disease and the stage of disease for the cure of which implantation is done. The cause of death of the donor is of vital importance. The safest subject is one dead of violence. Subsequent experience may show the safety of using glands removed from subjects dead of various diseases, notably nephritis and disease of the heart. Let us hope for this, as selection restricted to subjects dead of violence greatly limits the possible supply of eligible material. Subjects dead of infectious diseases, or affected by malignant disease, whether or not it is the cause of death, and those of a known cancerous heredity especially, are to be avoided. Aside from their dangerous character, testes removed from subjects dead of general infection undergo softening and decomposition with astonishing rapidity. In general, subjects dead of either acute or chronic infectious disease are not promising sources of sex gland supply, for two reasons: 1. The possible danger to the recipient; 2, the lack of vitality of and the rapidity with which autolysis occurs in the glands from the donor. The future alone can show how far we may safely take liberties in this direction. I fancy that we can safely take none.

It should be borne in mind, however, that the conditions in which gland implantation is indicated are often such that even considerable risk would be justified. On the average, the dangers of infection cannot equal in gravity those of the formidable surgical operations that we daily perform, and implantation *per se* is not dangerous to life. Perfectly normal and entire testes and ovaries are not absolutely essential. Fragments of normal portions of gland tissue taken from sex organs may be utilized, where neither the subject nor the gland is affected by malignant disease, tuberculosis, acute or chronic infection—purulent or other. When the recipient of the gland is known to be syphilitic, syphilis in the donor may be disregarded. It possibly may even add to the value of the gland. The uninfected glands of patients dead of tuberculosis are likely to be especially valuable, if the applicability of the method to the treatment of tuberculosis should be proved. Theoretically, tuberculosis should be found to be an inviting field for sex gland therapy. The only theory of treatment of the disease that has stood the test of time is that of nutrition, first, last, and all the time. The inference regarding the indications for sex gland implantation is obvious.

In any general bacterial infection of chronic type there is systemic reaction of ordinary glandular, internal, and lymphatic secretion. The lymphatics, in the attempt to filter the toxic substances and the internal secretory glands, stimulated to hyperactivity, act in combination with the other defensive factors to overcome the infection. Sex glands taken from an individual who has developed a relative immunity to the infection by means of his natural physiological resistance, and thereby decreased the relative virulence of the infecting organism, theoretically should possess, *cæteris paribus,* special therapeutic potency. Transplanted to an individual suffering from the same disease, the hormone of such glands should increase cell resistance and stimulate to greater activity the physiological nutritive defensive cycle, thereby aiding in overcoming the infection.

In treating experimentally tuberculosis by sex gland implantation, we therefore may use glands taken from subjects dead of that disease. There probably is little or no danger of local infection if the glands are macroscopically sound. The ovary, especially, should be safe, for it rarely is affected by tuberculosis, and even in the testis primary tuberculosis is rare. The hormone from the internal secretion of the implanted gland might be less in quantity and inferior in quality to one from a normal subject, yet potent enough to restore the balance of nutritive defense against the tubercle bacillus.

The excessive sexual activity noted in many victims of tuberculosis is here worthy of consideration. Is there a relative excess of gland activity with excess hormone thrown out as a defense, with coincidental sexual excitation, or is the tubercle toxin itself a psychosexual stimulant? I would suggest that the Fauser-Abderhalden test might show some interesting results in this field.

In cases of complete castration in either sex, a double implantation is likely to secure the best results. Obviously, even admitting that a single gland is therapeutically sufficient, double implantation gives one hundred per cent. better chances of success. If impotence and sterility in the male, it would seem rational to implant an entire gland, not only from the viewpoint of the dose of internal secretion, but also because of the more profound psychic effect thereby attained. A successful anastomosis possibly might restore the procreative glandular secretory function. In certain cases of sterility in the female, where the secondary sex characteristics are not marked, or the general vitality is low and there are no mechanical pelvic impediments from malformation or disease, a large dose of ovarian internal secretion possibly may stimulate the recipient's ovaries and induce fertility. This also applies to certain males in whom spermatozoa are formed, but in whom they are small in number and feeble in vitality.

The age of the subject from which the sex glands are taken for implantation is of great importance. Subjects from about the age of puberty to twenty-five, or perhaps even thirty years of age, are best, as at this time sex gland function is very active. The younger the subject—below eighteen or twenty years—the less the danger of encountering syphilis, and the more active the propensity for growth after implantation. Obviously, the danger of syphilis is relatively less at a given age in the female than in the male. Glands from subjects much younger than pubescents eventually may be found to be of especial value in meeting particular indications, more especially as pubescence is not really necessary for the production of hormone.

Again, we possibly may secure good results from the implantation of glands taken from subjects of

relatively advanced age. Testes from donors of even the recipient's own age at least may prove effective. Advanced age is associated, not only with a senile quality of internal secretion, but also with a relatively deficient quantity. The successful implantation of a single generative gland would logically increase the supply of internal secretion by one third, with proportionate benefit to the recipient. The foregoing remarks apply especially to the male, in whom the procreative period—and probably also the internal sex gland secretory period—lasts much longer than in the female. In dementia præcox and allied conditions, a healthy gland taken from a subject at any age below middle life possibly may be effective, if, indeed, sex gland implantation should hereafter prove to be effective at all in such cases.

Racial distinctions possibly need not be drawn in procuring implantation material, unless anastomosis is proposed. Theoretically, sex gland activity is likely to be greater in certain donors than in others, merely because of racial qualities. There is even a serious question in my mind, however, as to whether the tissue and blood elements of the recipient of the anastomosed gland would not eventually overcome any racial potentialities that might exist in the spermatozoa secreted by the implanted gland. This I found experimentally to be true of skin epithelium in cross grafting skin in negro and white, in 1880, a result verified by other experimenters. It is possible, moreover, that even the potential individual and family characteristics inherent to the anastomosed sex gland would be similarly overcome.

Tuffier asserts that transplantation of the ovary from white to black and vice versa fails of success. My experience in this regard is limited to a single case. On March 18, 1914, I implanted in the axilla of a woman aged sixty-seven years, afflicted with senile dementia, an ovary from a mulatto woman of forty years, dead eight hours of disease of the heart. Although greatly shrunken, the implanted gland apparently is still living.

That the Wassermann test should be employed where practicable goes without the saying. It must be remembered, however, that no more than a single test can be made on a dead body, and the test alone cannot be relied upon to eliminate the danger of infection. If it is shown later that freezing of the sex glands does not seriously impair the chances of success in implantation, there will be no necessity for urgent haste in implanting the gland, the work can be done with deliberation, and a Wassermann always will be practicable.

The danger of syphilis is minimized by the probability that Treponema pallidum lives but a few hours after the death of the host. Freezing probably kills the protozoon within an hour or two. If, therefore, frozen, or even refrigerated, glands should be shown to be satisfactory for implantation, the danger of syphilis would be practically *nil*.

In passing, I would suggest that, from the hormone therapy standpoint, it would be interesting to study the results of cross implantation of the sex glands of male and female. The experiment, at least, is practicable. I report herewith (Case VI) a case in which I implanted a testicle in a senile female dement.[11]

As to any essential difference between the male and female sex gland hormones in their influence on sex development, I have this to say: The primary sex characteristics are probably laid down in the initial combination of the male and female generative gland secretions—i. e., ovule and spermatozoon—and are inevitable phenomena in embryological development. The hormone, apparently, merely determines by its activities the secondary sex characteristics. Once these have developed, it may be a matter of indifference whether the body cells, even those of the sex glands themselves, are fed with male or female hormone. Accepting this hypothesis, the ovarian hormone should be therapeutically effective in the adult male, and vice versa. Possibly the male hormone is more powerful and likely to be more effective than even the ovarian, in the sex gland therapy of the adult female.

The persistence of typical sex characteristics, sexual power and desire in animals castrated late, after the internal secretion has done its work—e. g., geldings—is here again worthy of note.

### APPARENT PHYSIOLOGICAL EFFECTS OF TESTICULAR GLAND IMPLANTATION.

With due regard to the difficulty of excluding the psychic element in therapeutic experiments, particularly as regards subjective phenomena, whether the experiments are of the autovariety or the hetrovariety, I will present the apparent results of my own self experiment. Apropos of the possible "psychic" element in my observations, several facts should be remembered: First, my experiment primarily was designed merely to decide the question of the feasibility of successful implantation of sex glands from a dead subject; second, the local discomfort, a certain degree of apprehension, and the inconvenience resulting from the operation were such as tended, during the early postoperative period, to offset undue optimism based upon subjective sensations; third, the apparent results were such as are logically compatible with our knowledge of internal secretions, particularly of the sex glands; fourth, the implantation *per se* practically was a success, even though the gland proper through faulty technic, or other cause, or inevitable biological handicaps, should not permanently endure; fifth, subsequent observations (Cases II and VII) verified the conclusions to which my autoexperiment led me, so far as the effects of the sex hormone on nutrition were concerned.

The phenomena I shall here record were, so to speak, by results. I present them for what they are worth, hoping to make more comprehensive observations in future work.

The transient exhilaration usually experienced from cocaine did not follow the use of the mixture of novocaine, quinine, and urea hydrochloride. Despite considerable pain and some natural apprehension as to local results, there began at the end

[11] Since the foregoing experiments were made my attention has been called to Steinach's unsuccessful experiments of ovarian implantation in castrated male animals. Steinach makes no comments on the hormone therapy usages of such experiments. (*Jahrbuch, 6 für sexuelle Zwischenstufen*, January, 1914.)

of twenty-four hours a marked exhilaration and buoyancy of spirits, lasting for about twenty-four hours, at which time considerable swelling of the operation field and adjacent parts had developed. Possibly the stimulation experienced was merely delayed action of the local anesthesia. I am of opinion, however, that it was due to the absorption of secretions from the semidecorticated gland, which absorption temporarily ceased synchronous with the development of inflammatory exudate about the implanted tissue, or because of temporary exhaustion of the supply, the gland not having as yet begun to function. This I will term the "initial dose" of hormone.

On the seventh day after the operation, I again became conscious of stimulation and buoyancy so marked that I took an undue amount of exercise, attending the theatre in the evening. It was on the day following that increase of local discomfort led to an attempt to remove the implanted gland. Following the traumatism incidental to removing half the gland, the sense of stimulation disappeared, to return on or about the tenth day. I suggest that the second period of stimulation was synchronous with the beginning of the establishment of vascular adhesions and consequent functioning of the gland, with absorption of internal secretion, i. e., what I will term the "secondary or physiological dose" of hormone. This was checked by the traumatic reaction induced in the implantation bed, but recurred as soon as this began to subside, and was marked for several weeks, being gradually replaced by what might be termed a normal consciousness of unusual physical and mental vigor.

While the sense of stimulation was at its height, ability to endure physical and mental labor with much less than the usual amount of rest and sleep was noted. This has gradually lessened, *pari passu* with shrinkage of the implanted tissue, but both physical and mental efficiency are still far greater than before the implantation.

Blood pressure seems to have been greatly modified. December 28, 1913, it was recorded at the Chicago Laboratory by Dr. Ralph Webster. It registered 140, which was essentially what it registered on numerous other occasions. February 1 and 10, 1914, it was taken by Doctor Michel, and registered 120. On February 18th Doctor Webster recorded it as 120. Doctor Michel recorded it again as 125 on February 23d and 28th. Doctor Dagg, at the Chicago Laboratory, recorded it as 125 on February 25th. Doctor Michel and Dr. John McKinloch, March 7th, recorded it as 120. Doctor Michel recorded it as 125, Doctor Dagg and Doctor Croy, as 128, March 24th, and Doctor Webster as 128 on September 5th. Two different instruments were used.

I present the foregoing record without comment, save to remark that the reduced blood pressure has been associated with increased mental and physical vigor, and was taken in each instance when I was working under "a full head of steam."

There was a distinctly perceptible change in the bloodvessels. A moderately varicosed condition of the veins of the legs and arms markedly improved. The temporal arteries, which had been decidedly and disquietingly prominent, became indubitably smaller, and their walls softer. *Pari passu* with shrinkage of the implanted tissue and diminution of hormone dose, the vessels have become more prominent, but by no means so prominent as before the experiment. There has been no change for the past two months.

A decided change in the heart action has been noted in a certain direction; I have been troubled for some years by frequent attacks of cardiac irritability, probably due to overindulgence in smoking, combined with mental overwork and the worry incidental to the exigencies of practice. Often palpitation on retiring prevented sleep for several hours. This symptom entirely disappeared and has not recurred.

While the dose of internal secretion was at its height, a very peculiar symptom was noted; my glasses seemed to be "misfits." I paid little attention to this, however, having no suspicion that the ocular disturbance bore any relation to the results of the experiment. As the same interesting phenomenon occurred in the case of ovarian transplantation shortly to be presented, I have concluded to record it here. The explanation of the symptom would seem to be a stimulation of the muscles of accommodation. The condition is still slightly noticeable in my own case. A test of accommodation by Dr. J. E. Colburn, May 14, 1914, showed it to be practically the same as at his last examination, nearly four years ago. There has been, if anything, a slight increase in the range of accommodation.

There has been an improvement in the circulation of the skin, so marked as to excite comment by persons who had no knowledge of the experiment. Incidentally, resistance to cold appears to be increased. The hemoglobin record, which had ranged from ninety to ninety-five for some years, since the implantation has been 100 plus. As no test had been made for some time prior to the experiment, this deserves no special emphasis, yet it might not be amiss to call attention to Case VII.

The effect of the implantation on the sexual function was merely what might have been expected from local irritation in any normal individual at the same period of life. As to what might result in cases of impaired sex function, no deductions can be drawn from this particular experiment, save that the psychic effect of reflex stimulation and the increase of tone should be markedly beneficial. Case III is more to the point.

As to what might result from a dose of internal secretion larger than that afforded by the portion of gland still remaining *in situ,* in a person whose mental faculties are not under stress and preoccupation, a definite opinion would be premature, but a decidedly stimulating or perhaps permanently tonic effect should logically be expected, judging by the report of my second case of testicular implantation shortly to be recorded (Case III), and judging by our knowledge of the relation of general well being to sex vigor, and the marked improvement in physical and mental efficiency resulting from a moderate dose in my own experimental case.

Supplemented—where indicated by the mechanical vascular conditions—by resection of the vena

dorsalis penis, as modified by myself, successful sex gland transplantation should not often fail to relieve impotence where serious brain or cord disease does not exist.

There has been an increase of ten pounds in weight, which may or may not be significant.

Brown-Séquard noted a pronounced stimulation of the function of the bowel following the self administration of his animal extract. As a victim of a rather constipated habit, I regret that my own experiment was not attended by a similar result.

The most remarkable apparent result of the implantation is the following: In 1898, following a septic wound and an attack of grippe, followed by appendicitis, for which I was operated on, September 10, 1899, by my friend, Dr. Robert T. Morris, of New York, I acquired an epithelial nephritis. From this I recovered under the care of my friend and colleague, Dr. William E. Quine. Since that time, however, I had been somewhat annoyed by marked edema of the lower extremities appearing at the end of the day, and often persisting during the entire twenty-four hours. This gave me considerable anxiety for some years, but as my general health became excellent, the kidney difficulty disappeared, and there were no heart complications, I ceased to concern myself about it. There also had existed, for fifteen years or more, a marked keratosis of the soles of the feet, which, combined with an eczematous condition of the flexures of the toes, gave me much annoyance. At one time I consulted my friend, Dr. Joseph Zeisler, regarding it. Nothing seemed to benefit the condition, and I finally abandoned the idea of curing it, contenting myself with the occasional application of palliative ointments. About four weeks after the implantation experiment, the skin of my feet had become normal, with an unusually healthy color. Doctor Zeisler examined them on February 27, 1914, and remarked that the skin was as soft and flexible as that of a young person. No remedial applications of any kind had been made for several months. Possibly it may be contended that the improvement in the condition described was nothing but a coincidence, but it certainly must be admitted that it is not incompatible with the probable effects on nutrition of internal sex gland secretion. (Note also Case VII.) Granting for the sake of argument, that the change in the skin really was due to the internal secretion of the implanted gland—and this I feel positive is the true explanation—what may we not expect from the action of internal secretion on the bloodvessels? Indeed, judging from what probably resulted in my own vessels—and from a small dose—and in Case II, should a definite action of sex hormone on the bloodvessels be proved, victory over senile changes may not be an enthusiast's dream, and old age may come to be regarded as in a sense a curable "disease."

September 5th, 1914, the keratosis has not returned, and the skin is still normal, save at the borders of the soles, where in certain limited areas it is dry and slightly eczematous. Following a recent attack of digestive disturbance of several weeks' duration, there has been a slight recurrence of edema of the legs.

From my experience in my own case I was inclined to believe that psoriasis and kindred diseases were due to perversion of internal secretion. The results of sex gland implantation in Case VII have impelled me to the firm conviction that this theory of their etiology is well grounded. As to the possibility of the cure of certain chronic diseases of the skin, the general principle is self evident, and no comment is necessary.

I regret to say that no careful observations of the effects of the implantation on the heart and respiration were made during the progress of the experiment. Cursory observation of the pulse showed a beat temporarily rather higher than my normal average, but this may have been purely neurotic and is merely worth casual note.

(*To be continued.*)

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## A CURETTE FOR THE ENDOTYMPANUM.

### *To Be Used in Treatment of Chronic Suppuration of the Middle Ear.*

By Edward L. Meierhof, M. D.,
New York.

As a contribution to the equipment for the treatment of tympanic disease, especially the epitympanic and hypotympanic spaces and the Eustachian tube, I wish to offer a curette which has given me most excellent results. The idea was borrowed from Dr. F. Skeel's instrument, which he used with success in shredding out the sac of a Meibomian cyst. I have adapted this instrument to the treatment of middle ear suppuration.

The curette is a serrated cup on a flexible shaft, and is made in two sizes; the larger for the removal of polypi and prominent granulation masses, and the smaller for the tube and crevices. With this instrument the operator can enter the Eustachian tube, the epitympanum, the hypotympanum, and

Fig.—Middle ear curette.

work over the promontory without fear of injuring the round or oval fenestra. When working with it, the operator must be able to see very definitely what it does, while groping in the dark is inexcusable.

The curette is held lightly between the thumb and forefinger, and its bowl is applied very gently so as to shred over the diseased parts. The ease with which these curettes can be employed, and the results that follow, will be found very gratifying. As no violence in the way of pressure, etc., is required, the reaction is not severe. Occasionally the operation will have to be repeated, but in most instances a single curettage suffices.

In removing polypi this curette enables one to dispense with the snare, an instrument which, by the way, I regard as a very hazardous one, and believe that at times meningitis has been induced by the evulsion of polypi with it.

Aftertreatment with dry wipes of cotton on toothpicks, or dipped in alcohol or nitrate of silver, either in solution or fused on a probe, may be necessary. Anesthesia is obtained by introducing into the tym-

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## Original Communications.

### NERVE BLOCK, PUBLIC HEALTH, AND TUBERCULOSIS.


BY SIR JAMES GRANT, K. C. M. G., F. R. C. P. (LOND.),

Ottawa, Canada.

President, Ottawa General Hospital, and Chief of Staff.


Public health is now calling forth much merited attention, and very fortunately so, as valuable life is thus saved, and the foundation of national prosperity established. The first question which arises is, Are we making distinct and satisfactory progress in our sanitary measures?

In England, after the Restoration, for fully twenty years, there was a high degree of mortality throughout the kingdom, which Macaulay described as a time when men died faster in the lanes of the towns than they died on the coast of Guiana. as the rate of mortality in London, from 1660 to 1679, was not less than eighty in the thousand. Fortunately a few years exercised a remarkable change for the better, as from 1846 to 1855 it was reduced to 21.9 per mille; and in 1871, to 22.6. In England and Wales the death rate in 1912 was 13.3 per mille, twenty-seven per cent. less than the mean yearly rate during the period 1891 to 1900. The death rate is much in proportion to the density of population. Man has no control over the laws of nature, but if we live in compliance with these laws, we more and more appreciate that they are charmingly arranged for the promotion of health and the prolongation of life. The health of the nation stands in close relationship to the individual. When the waste of the component parts of the body is greater than the power of restoration, then is the time to observe closely the indications of bodily decay; in the evident want of balance between waste and supply, there is an undoubted wornout condition of the system.

The essential requirements of communities and individuals must be and really are the same. Individuals must be well clothed, well fed, well housed, well aired, and well watered. Public health is a simple problem, yet frequently its attainment is difficult. A great part of sanitary science can be stated and comprised in one word—*cleanliness*. Clean houses, clean air, and clean water are a remarkable trio of power in establishing genuine sanitary conditions.

The ancients fought against bad smells most vigorously and endeavored to mask odors with perfumes. In fact at the present day, scents abound frequently to suppress filth. Ancient Capua had streets of perfume shops with that object in view. There is little of originality in our efforts in public health. Moses was a most practical hygienist, and one of the most telling and far reaching commandments he brought down from the Mount was *Thou shalt not pollute rivers*. In fact the ancients knew as well as we of the present day, the conditions of public health—foulness a source of disease, and cleanliness a preventive. Wash and be clean is actually the sum and substance of sanitary science. Physical and moral purity is next to Godliness.

In 1665, when the Court and Parliament of England assembled at Oxford, it had an immunity from plague, traced to the thorough cleansing which the magistrates gave to the city, to insure safety for its distinguished guests, confident that public health could be assured only by cleanliness. These are our lessons today.

Hippocrates, the first hygienist, gave to science an entire volume on public health, and his chief text was pure air, pure water, and pure soil, the adopted maxim of the present day after centuries of careful inquiry. Napoleon at St. Helena stated, "Life is a fortress which we know little about. Water, air, and cleanliness are chief in my pharmacopœia." Really today our knowledge of air and water is not complete. Nature is an object lesson in hygienic arrangements, which if followed carefully, will be productive of most gratifying results.

Canada delights in the scenic beauty of its rivers, and we trust the prospect of their being converted into open ditches, polluting the districts through which they flow, will by legislative enactment shortly become a matter of the past. Ottawa has suffered from an epidemic of typhoid fever, so we look forward to a supply of water which will not require purification, and so contribute health, happiness, and prosperity to our people.

Disraeli, in a celebrated speech at Manchester, pledged himself that a conservative Government would devote special attention to sanitary subjects. He said, as Prime Minister of England, "I cannot impress upon you too strongly my conviction of the importance of the legislature and society, uniting together in favor of these important results."

The Right Honorable Joseph Chamberlain, whose death the whole British Empire is now mourning, was deeply interested, while in public life, in the health and welfare of his people, and we can well pay a tribute to his memory for the remarkable breadth of view which enabled him to define the close connection between successful colonization of

an inhaler, 1, simple in construction; 2, simple to learn to use; 3, sparing of ether, and, 4, safe in the hands of the most inexperienced, layman, midwife, nurse, or doctor; 5, sanitary, in that it can be easily taken apart, sterilized, and reassembled.

The inhaler herewith presented represents the evolution of the Allis inhaler to the more simple, safe, saving, sanitary model of 1912, which was presented November 28, 1912, to the Medical Association of the Greater City of New York. (*Year Book,* June, 1913, p. 46.)

In 1892, the sleeve was lengthened from six to nine inches to allow the upper part to be folded over and keep the ether from escaping so freely, and to heat the ether before it entered the lungs. In 1894, we did away with the interlaced bandage, substituted a gauze diaphragm at the lower end, and inserted a small piece of gauze loosely in the centre to receive the ether. (*International Journal of Surgery,* XII, 223, 1899; *Medical Record,* December 30, 1899.) But this plan did not afford the needed evaporating surface so essential for rapid entrance and absorption of ether in the lungs.

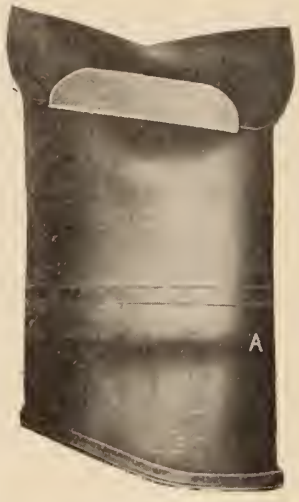


Fig. 2.—Rubber sleeve with flap for closing the top; A, projecting cord inside to hold the drum well above the nose.

The inhaler now consists of two parts: 1. An oblong, *metal drum* (Fig. 1), two inches wide, four inches long, and three and a half inches deep. Its sides are without fenestræ. The drumheads are formed by slipping the drum sidewise into a six inch piece of an old stocking, or small stockinet such as is used for the kneecap; or by winding over the ends of the drum with a gauze bandage so as to cover them with eight thicknesses of gauze, securing them in place by rubber bands, pinning, or strips of rubber adhesive plaster. When thus properly covered, the drum is inserted into its *rubber sleeve* (Fig. 2), five and a half by nine inches, on the top of which has been added a flap or tongue; and inside the sleeve it forms a chamber, near the bottom a corded ridge, wherein the ether can be rapidly evaporated and heated before being inhaled and thereby guards against postanesthetic bronchitis or worse. The flap can be thrown from side to side, opening the top, for dropping in more ether or securing greater heating and concentration of the amount inhaled. This also leaves the right hand free for other uses. The plate on the flap is to weigh it down.

The drum can be made from a three and a half inch length of four inch leader pipe, bent into an oblong, covered with stockinet or wound with gauze, wrapped around with newspaper to form the sleeve, and stitched or pinned together. We have used thick cardboard and a towel. From the foregoing, after so many years' experience, we deem it justifiable to hold that the Gallant inhaler is simple in construction; any novice can make one and use it; with ether, chloroform, or in combination, but for chloroform the *top must always be kept open.* It is safe, whether the ether is poured in, or by the drop method, the double drumheads will prevent its running down into the throat, afford a large area for rapid evaporation, and the sleeve acts as a heating chamber, preventing bronchitis or worse. The inhaler is also saving. The cost is very small; it requires no express wagon to transport it; the quantity of ether during the first hour averages 100 c. c. less, when preceded by hypodermic of hyoscine, morphine, or the oil of bitter orange peel (Gwathmey, New York Medical Journal, September 14, 1912; November 29, 1913), and the patient goes under with much less excitement.

Nitrous oxide or oxygen may be introduced at the top or bottom, for primary anesthesia or stimulating purposes. The inhaler, finally, is sanitary. The drum is easily removed from the sleeve, the drumheads are readily changed, and, after cleaning and drying, it can be sterilized, quickly replaced, and dropped into the operating bag, ready for immediate use.

70 East Sixty-sixth Street.

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## IMPLANTATION OF THE GENERATIVE GLANDS AND ITS THERAPEUTIC POSSIBILITIES.

*Successful Autoimplantation of a Testis from a Subject Dead Twenty-four Hours. Other Successful Implantations of Testes and Ovaries from Dead Subjects. Experimental Implantations in Various Conditions, and Cross Implantations of Testes and Ovaries Taken from Dead Subjects.*

By G. Frank Lydston, M. D.,
Chicago,
Formerly Professor of Genitourinary Diseases and Syphilology, Medical Department, State University of Illinois.

(*Continued from page 819.*)

Carrel and Guthrie assert that transplanted exogenous glands can function only temporarily. The kidneys of the cat, transplanted in the same individual, survived. When transplanted from one living individual to another, they excreted urine for three weeks, at the end of which time they ceased secreting and the animal died. This has little bearing on the exogenous transplantation—at least for therapeutic purposes—of the sex glands in the human being.[12] The sex gland, by virtue of its internal and external secretory structures, is a more highly specialized organ than the kidney. It is also a doubly functioned organ. The kidney is distinctly an excretory organ, while the testis and the ovary are not, in the true sense of the word. The true generative secretion in either sex is not thrown out for elimination as useless or toxic matter, but, on the contrary, its physiological function does not begin until after the discharge and organic union of the secretions of the two sexes. The organs

[12]See my Case VI.

which produce the generative secretion are more active, more highly organized, and more energetic than the kidney. So highly specialized are their functions that no other organ can act vicariously for

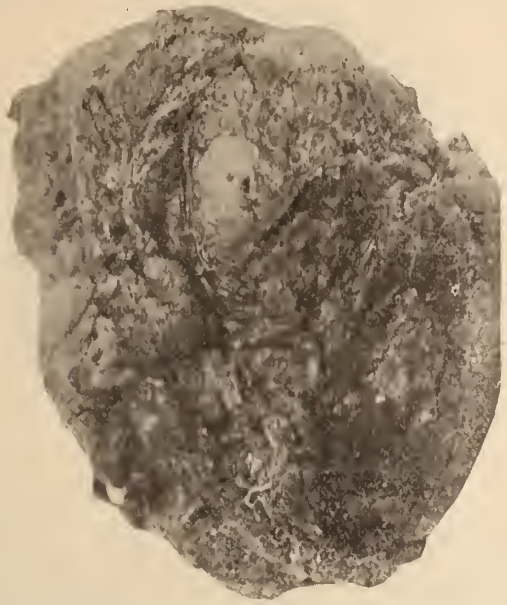

FIG. 1.—Showing posterior border of implanted testis, with site of removal of epididymis, (A) and extensive vascular areas. (Case VI.)

them, as can the skin and bowel for the kidney. When the generative secretion ceases or is prevented from escaping from the sex glands, the organs still function importantly—producing hormone.[13]

Again, as stated elsewhere in this paper, even though the implanted gland should finally perish, its work of cell regeneration has perhaps been to a

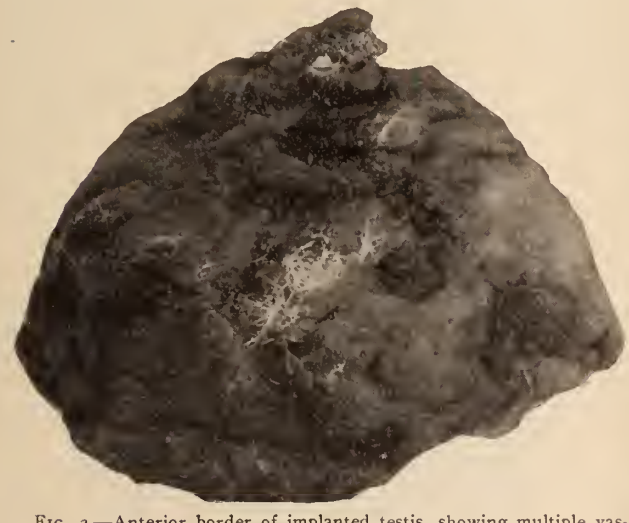

FIG. 2.—Anterior border of implanted testis, showing multiple vascular areas. (Case VI.)

greater or less extent accomplished, with beneficial results which may be permanent. Then, too, apparent atrophy does not necessarily mean that the interstitial cells (Leydig) are destroyed. Considerable diminution in bulk even may occur from various causes without the generative function itself being destroyed.

[13]E. Ullmann, *Annals of Surgery*, August, 1914, reports a case of functionally successful anastomotic transplantation from one dog to another.

That the conditions are different in the two varieties of gland is shown by comparing the results of Carrel's and Guthrie's lower animal kidney transplantation experiments with my own autohuman and heterohuman sex gland implantations. Theory aside, I believe that my experiments have conclusively proved that, as regards formation of new blood supply and survival of the hormones pro-

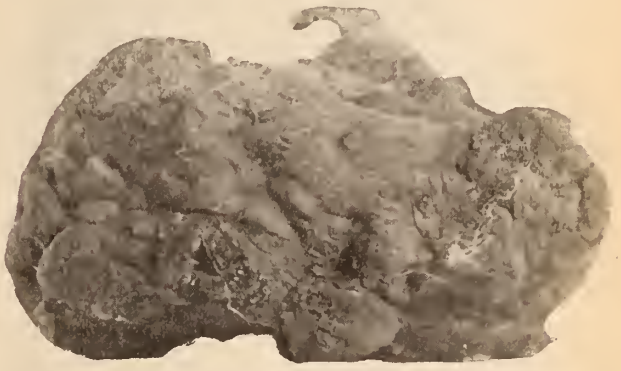

FIG. 3.—Lateral view of implanted testis with numerous vascular areas (Case VI).

ducing cells and internal secretion therapy, transplantation of sex glands, even from the dead body, is both practicable and successful.

As to Carrel's belief that practically the only hope of success in gland transplantation in general is in a close blood relationship of donor and recipient, the author believes that, while such relationship is highly desirable, he has proved that it is not essential to either sex gland hormone therapy via implantation[14] or survival of the essential elements of the gland. It is noteworthy that Carrel and Guthrie's conclusions from their experiments on the kidney of the cat, if accepted as final in their bearing upon gland implantation in general, would reduce to a minimum the practicality of Carrel's own discovery of the persistence of tissue vitality after somatic death, so far as its application to the hormone treatment of disease is concerned. Apropos of implantation of testes from distinctly alien sources Guthrie[15]

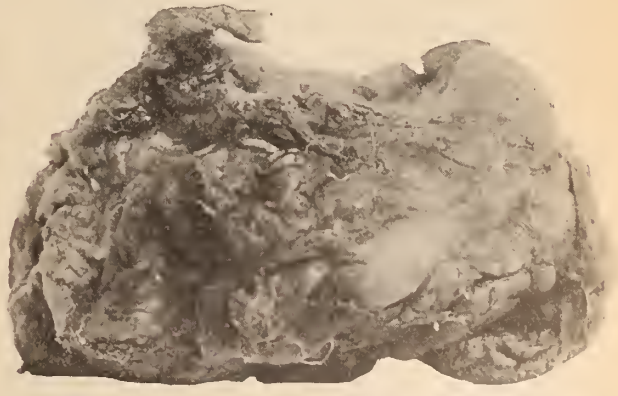

FIG. 4.—Lateral view of implanted testis with numerous vascular areas (Case VI).

reports a case of transplantation of a testis of a guinea fowl to the shoulder of an ordinary domestic cock. The implanted tissue disappeared. In pass-

[14]The author has further confirmed this view by experiments on fowls.

[15]*Journal of Experimental Medicine*, xii, 1910.

ing, it might be interesting to Doctor Guthrie, if he has not already made the observation, that it is possible to crossbreed the guinea fowl and the American game fowl, hence they are not as alien to each other as might be supposed. I saw, a little over a year ago, a bird, apparently a male, so bred on

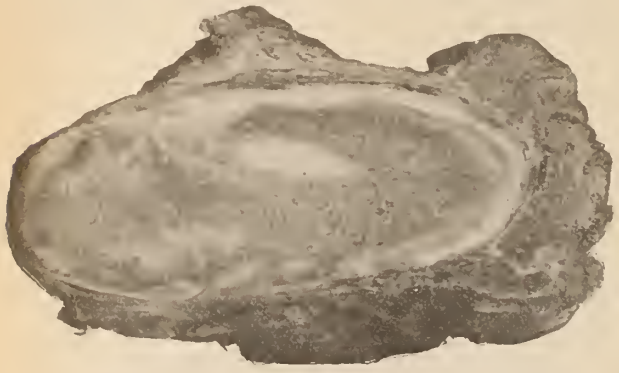

Fig. 5.—Longitudinal section of implanted testis. (Case vi.)

the farm of Mr. H. B. Gleezen, the well known game fowl breeder, of Georgetown, Mass. I recently transposed the testes of a Chinese pheasant and a domestic fowl, the results of which will be noted at some future time.

The exogenous transplantations of ovaries from the living to the living in sheep and guineapigs, reported by Voronoff and Castle, support Carrel and Guthrie's conclusions, but there still remain the questions: 1. Whether different results may not occur in human beings; 2, the possible therapeutic value of implantations of human sex glands, with or without permanent life and function of the cells of Leydig, even though generative tissue atrophy inevitably should occur.

Case II. *Successful implantation of ovary from a subject twenty-three hours after death.* Mrs. J., aged fifty-nine years, suffered from the nerve wreckage incidental to a pelvic operation performed fifteen years ago, and also from hepatic and gouty disturbances. The uterus and appendages were removed. A "piece of the ovary" was said to have been preserved. I explained to this woman the objects and experimental nature of ovarian implantation, and she was brave enough to submit to the

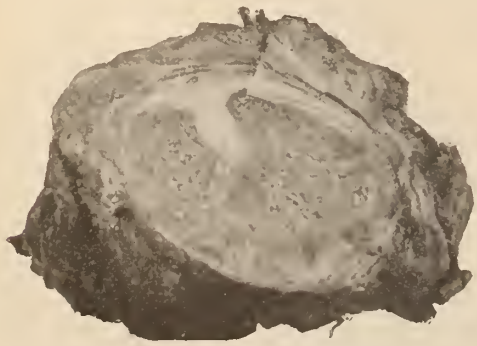

Fig. 6.—Transverse section of implanted testis. (Case vi.)

operation. Too much praise cannot be bestowed on her for cooperating in the experiment.

The implantation was performed March 3, 1914. Ovaries were taken from an apparently healthy girl of sixteen years, a *virgo intacta,* dead twelve hours of skull fracture. The operation was performed eleven hours after the removal of the ovaries from the subject, and twenty-three hours after death, Doctor Michel assisting. One ovary, the left, was implanted in the left labium majus, this location being selected because of the obesity of the patient, and my desire to study the local results of the implantation. There was no marked tissue reaction, only slight tenderness, very little pain, and no rise of temperature, the wound healing by primary union. The patient was up and about on the fifth day, reporting at my office on

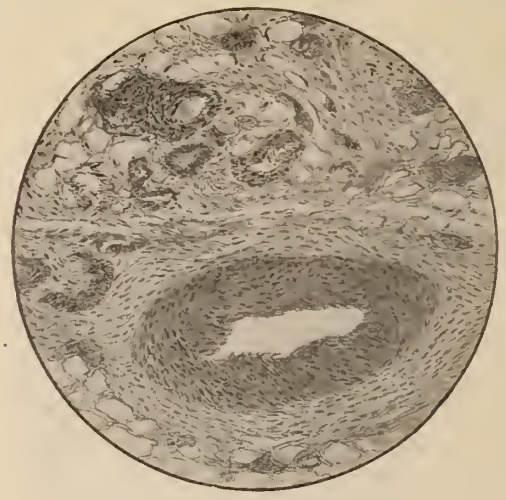

Fig. 7.—Bloodvessels, connective tissue, and fat in periphery—tunica albuginea—of implanted testis. (Case vi.) (⅔ in. objective.)[1]

the ninth day. She might have been up sooner but for a persisting vaginal prolapse and vesicocele since the operation of many years ago, which required self inserted tampons to permit locomotion. May 14, 1914, the implantation appeared to have been successful, the ovary was still *in situ,* and of course, "living." On April 27th, the case was examined by Dr. William E. Quine, who stated that the implanted ovary was still distinctly to be felt. Dr. Alice Conklin, Dr. Effie Lobdell, and Dr. Ethel Rice also observed the progress of the case until May 30th, at which time the improvement still persisted and the ovary was still plainly perceptible.

It is unnecessary to state that Mrs. J. underwent a severe test of implantation. After fifteen years of neuropathy and loss of sex function, with other disturbances alien to the latter, a great deal was not to be expected of the method. A complete failure of therapeutic results would not have disproved the

Fig. 8.—Numerous new bloodvessels, fat, and connective tissue in and beneath the tunica albuginea of implanted testis. (Case vi.) (⅔ in. objective.)

efficacy of implantation in general. The same may justly be said of Experiments iv and v. Further-

[1]The sections were prepared by C. E. M. Fischer, M.D.; the drawings by Zan D. Klopper, M.D.

more, the results of ovarian implantation, whether favorable or unfavorable, in such cases, constitute, not a positive indication, but merely a suggestion of what possibly may be accomplished by testicular implantation in the male.

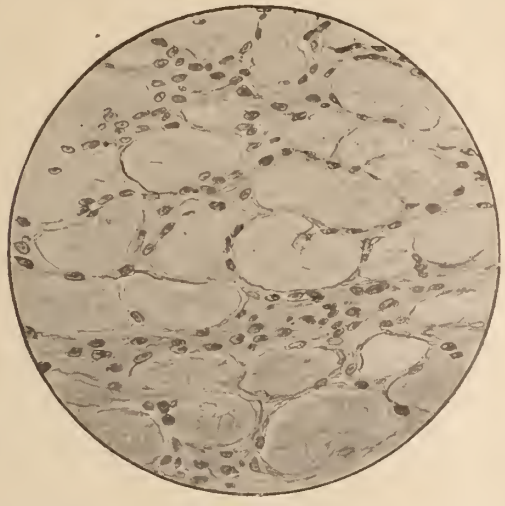

FIG. 9.—Showing area of probably dead, and another of distinctly vitalized tubuli seminiferi with an abundance of living interstitial cells in implanted testis. The vitality of the glandular tissue and the quantity of interstitial cells increases from the centre toward the periphery of the implanted gland. (Case VI.) (⅙ in. objective.)

*Apparent results in Case II.* While appreciating the fact that it is yet too early to determine permanence of the physiological results of the ovarian implantation, and making due allowance for psychic effects, I will present the report of the patient and her family. Briefly, this is as follows: There was a marked exhilaration for the first few days, interrupted one morning by what the patient termed a "slight nervous chill." On the seventh day she complained that her glasses seemed to be no longer effective, and that she could not see with them to read or crochet. She then asserted, and appeared to demonstrate, an unwonted flexibility and comfort of action of her knees which, she said, had been "stiff and lame for

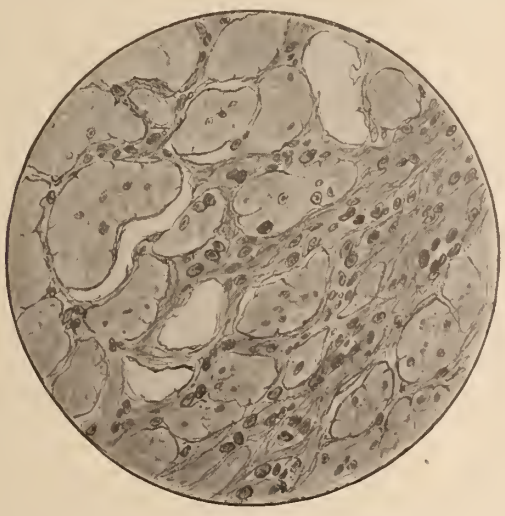

FIG. 10.—Section near periphery, also showing gradual increase of vitality of gland tissue from the centre toward the periphery of implanted testis. (Large amount of interstitial tissue. (Case VI.) (⅙ in. objective.)

several years." Her hot flushes disappeared. She no longer experienced an almost constant sense of exhaustion, and arose refreshed in the morning, whereas she stated, she formerly arose as tired as when she went to bed. Like myself, she stated that she needed less sleep. She was formerly annoyed by somnolence on inappropriate occasions. This disappeared. Having in mind the "initial dose" of hormone, I am inclined to credit the patient's statements as to early effects. Blood pressure was not changed ten days after the operation.

After the first ten days, the patient gradually lost the primary effects. March 24th, however, she reported great increase in physical endurance, stating that she could climb

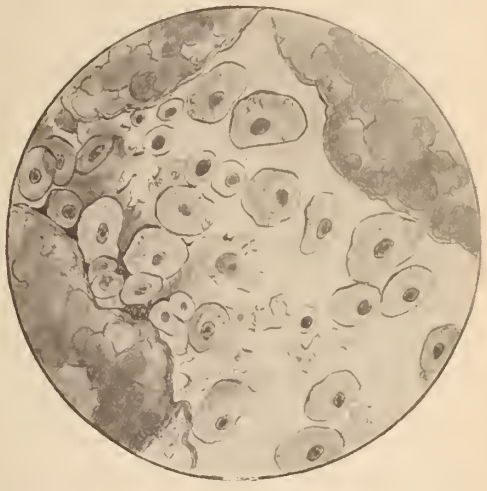

FIG. 11.—Free and attached interstitial cells with contiguous tubuli seminiferi in implanted testis. (Case VI.) ($^1/_{12}$ in. objective—oil immersion.)

three flights of stairs without discomfort or cardiac disturbance. Formerly she was compelled to aid herself by holding on to the baluster. She reported again, great increase in physical endurance, with improvement in the digestive functions and complete disappearance of the joint stiffness and of a feeling of numbness and coldness in the limbs associated with uncertainty of locomotion which had troubled her for some years. Blood pressure still was unchanged. Complete relief of constipation of many years' standing was also reported. Four weeks after the implantation, there was a marked change in blood pressure, which Doctor Michel reported to have afterward ranged from 125 to 130. On April 27th, Dr. Ralph Webster recorded it as 125. May 14th, I recorded it as 125. Two different instruments were used in making the

FIG. 12.—Section from area of periphery of implanted testis, corresponding with site of the epididymis, showing vein containing blood and vasa efferentia. (Case VI.) (⅙ in. objective.)
There were no areas of softening or of fatty degeneration in the interior of the gland. The Sertoli cells could not be distinguished.
The sections were prepared by C. E. M. Fisher, M.D.; the drawings by Zan D. Klopper, M.D.

record. Dr. Harry S. Gradle, who had been making a study of Mrs. J.'s case accommodation, reported that it had improved remarkably while the patient was under his observation—a period of four weeks.

The patient made a severe test of her physical condition during her spring housecleaning, and experienced only the normal degree of fatigue. She stated also that an obstinate, frequently recurring bilateral sciatica of over thirty years' standing had entirely disappeared. About July 1st, she had a moderate transient, unilateral recurrence, following mental disquiet. At present writing, August 1, 1914, the improvement in the subject's condition still endures. The implanted ovary, although diminished in size, can still be distinctly felt. Blood pressure September 10th, is 128. The condition of the bowels is not so good as at previous report, although still better than before the implantation.†

Case III. A man, aged fifty-eight years, commercial traveler, who, for a period of five years had been under my observation from time to time for partial atonic impotence, consented to submit to testicular implantation. There was no local disease or abnormality. Somewhat less than half of a testis was implanted, the material used being obtained from the body of a man, aged thirty years, ten hours after death produced by contact with a live wire, being a portion of a gland the remainder of which four days later was used in a cross implantation, the remainder of the gland also being used in a case of anastomosis. The implantation was performed thirty-six hours after the death of the donor. The recipient was somewhat neurasthenic, as naturally was to have been expected, but was apparently in excellent health and well preserved for a man of his years.

The implantation was performed, March 14, 1914, Doctor Michel assisting. The portion of gland was partially decorticated and implanted in the left side of the scrotum, in contact with the cord, immediately posterior to the testis of the recipient, the technic being essentially the same as that employed in my autoexperiment. There was only moderate reaction after the implantation. This had subsided by the twelfth day, at which time a moderately firm, circumscribed, movable mass of glandular outline could be felt at the site of the implantation. During the process of healing the patient expressed himself as conscious of a remarkable stimulation of sexual activity. According to his account of the subjective symptoms, this began almost immediately—four or five days—after the implantation and continued during the progress of healing. Obviously the psychic element must be considered in connection herewith, as there was very little inflammatory reaction and the patient was not at all apprehensive of accidents. Nocturnal erections began on the second night after the operation and recurred regularly while he was under my observation. On the fourteenth day the patient left the city. A letter received from him, June 15th, was worthy of note merely as bearing upon his condition at that time. Quoting this letter, the points of interest are: ". . . The erections at night have continued regularly. They have rarely occurred before during the past four or five years. The erections are not quite as strong as in my younger days, nor so long continued, but the sexual act is natural again and is not followed by great exhaustion as was formerly the case. . . . The lump where the piece of gland was planted has shrunk somewhat, but I feel sure that the gland is alive and hearty. . . . I am still feeling fine and much more vigorous than I have felt for years." The evident improvement in this patient's sexual function cannot reasonably be entirely explained by the psychic effect of the implantation. Nocturnal erections dissociated from the erotic dreams do not occur from purely psychic impressions. As to the influence of local irritation, this might explain the sexual stimulation occurring immediately after the operation, but naturally it would have subsided later. The question of permanence of results can be settled only by time.

On July 20th, this patient presented himself for examination. The implanted mass of gland tissue was still perceptible and about the size and shape of a good sized almond. He asserted that the improvement in sexual vigor still persisted. No observations were made of the physiological effects of the implantation in this case, save to note the blood pressure—which was 165, and has thus far undergone no change—and to examine the semen microscopically, which was normal, July 20th.

†Recently following a severe nervous shock, the condition of this patient became very unsatisfactory. She is, however, now again improving.

February 21, 1914, Dr. Bayard Holmes, of Chicago, called my attention to his masterly paper, The Nonmental Character of Dementia Præcox (40), on reading which I was interested to note that Fauser's experiments in the diagnosis of dementia præcox and allied conditions, which experiments had not previously been brought to my attention, were complementary to the theory on which I had been working, in endeavoring practically to administer internal sex secretion in various conditions. Following Abderhalden's theory of "dysfunction," Fauser (41) found that the *Abwehrferment* or defensive ferment in the blood of patients with dementia præcox reduced the antigenlike material made respectively from the testicle or ovary, according to the sex of the patient. He finally established his test as a reliable diagnostic procedure. Summing up his studies of the Abderhalden test and its application to the insanities, Holmes says:

1. The evidence accumulated taken with many other factors indicates that dementia præcox is a condition or disease in which the secretions of the genital glands are greatly perverted.
2. As a part of this disturbance of the balance of the internal secretions, many other glands are coincidentally disturbed.
3. This "dysfunction" of the genital glands may be and is likely to be due to various peripheral infections, such as are found to produce dysfunction of the thyroid.
4. The Abderhalden reaction promises a method of diagnosis which can be applied early, in pedagogic and penal, if not judicial laboratories.
5. The psychogenetic theory of dementia ought to stand aside and give way to research into physical conditions and etiological factors and methods of prevention and cure.
6. Every institution that makes any pretence to psychiatry, even every reformatory for juvenile offenders, male or female, should have a laboratory fitted out for the defensive ferments reaction.

Adding to the list of causes of dysfunction imperfect or aberrant sex gland development, leading to dementia præcox and allied conditions, the etiological picture is complete.

*In the light of Fauser's observations, the conclusion is obvious that the logical indication in dementia præcox is the administration of internal secretion, or a combination of secretions. In implantation of sex glands we have the most logical method for the administration of probably the most important of all the internal secretions in the field of psychiatry.*

If the essence of etiology of dementia præcox really is a dysfunction of the sex glands, then the indications are especially clear and logical. It must be remembered, however, that, although it is conceded that the indications for sex gland implantation seem to be especially clear in dementia præcox, by the time the diagnosis is made, considerable organic neuron change may have occurred, with a resulting permanent aberration of function. Unlike other organs, probably compensatory action of brain cells will not occur and conserve its mental functions. A moderate impairment of the structure of the hepatic or of the renal cells may not be manifested by any apparent change in the health of the subject. In the case of the kidney, vicarious action of other eliminative areas may indefinitely keep the subject in apparently good health. The slightest impairment of the delicate, highly specialized brain neuron structure, will almost in-

evitably be followed by a greater or less degree of mental deterioration.

The hebephrenic type of dementia præcox probably is the most promising one for hormone therapy. While diseases of the nervous system in general seem to be a promising field for sex gland secretion therapy, early administration is urgently necessary to give both the patient and the remedy a fair chance. Regeneration of structurally damaged, delicate neuron, nerve fibre, and ganglion cell is rather more than can fairly be expected of any remedy.

In the early stages of locomotor ataxia and paresis, implantation seems to be worthy of trial. The disastrous effects of the spirochete are largely due to the cell toxemia it produces, and to the pressure of vascular cell infiltration. The resulting damage is of a nutritional type, and the indications seem to be clear enough.

Chronic inebriety offers considerable inducement for sex gland therapy. The innutrition and nerve instability which cause the cell to "cry" for alcohol, quite likely can be met by the hormone of the sex gland secretion, administered in one form or another, preferably, perhaps, by implantation.

Given a remedy which really stimulates the nutrition of nerve tissue, and the possibilities of service in therapy are boundless. There are few chronic diseases in which the nervous system is not more or less involved, with resultant trophic, sensory, or motor perturbation.

Apropos of the possible benefit of internal sex gland secretion in arterial conditions in which syphilis is the primary etiological factor, the analogy between senile and syphilitic vascular changes is suggestive.

In enlarged prostate, benefit might occur from sex gland implantation through, 1, relief of the senile etiological element through improved nutrition; 2, antagonism to the bacterial infection element—gonococcic or colon—which is such an important etiological factor in prostatism.

In dementia præcox the etiological possibility of syphilis should be seriously considered before resorting to implantation. Here the Wassermann test is of great service. Syphilis is unquestionably responsible for some cases of dementia præcox, or at least of a certain proportion of cases which fall symptomatically under that nomenclature. I qualify merely because the Fauser-Abderhalden test may force the adoption of a new nomenclature.

In a case of a boy of twenty years, seen about five years ago, in consultation with Dr. C. R. Burr, a most competent alienist of Flint, Michigan, I diagnosed syphilis. The Wassermann test proved negative. No history of syphilis had been recorded. During a fairly lucid interval, the patient finally related to me an escapade of intoxication and exposure to infection, a promptly and mistakenly cauterized penile sore of brief duration appearing later. Careful inspection showed a fairly typical adenopathy and a sparse, fading roseate papular syphilide. The patient recovered under specific medication and is now apparently perfectly well. As a presumptive verification of the diagnosis, a retinal or choroidal hemorrhage occurred, undoubtedly because of neglect of treatment, some months ago, destroying the vision of the affected eye.

It may be remarked that syphilis in the recipient ought not to be regarded as a contraindication for implantation. The disease may act as other infective diseases apparently do, by a toxic influence on the internal secretory function of the sex glands. Antisyphilitic treatment is indicated, but the impression made by the infection upon the sex glands may be such that treatment is ineffective. Here gland implantation is worthy of trial.

Senile cataract and its associated conditions in their incipience are an attractive field for experimental work with the sex gland hormone via implantation.

Should sex gland implantation prove even moderately effective in checking or improving the conditions incidental to at least a moderate proportion of cases of senility, arteriosclerosis undoubtedly will be considered amenable to treatment. As to incipient senile dementia, the inference is obvious, and I believe this to be a very promising field. Possibly certain types of prostatovesical disease and chronic rheumatoid affections of the joints also may prove amenable to treatment.

The thought occurs to me that the sex gland hormone possibly might increase the resistance of the brain cells to toxins and improve their nutrition sufficiently to correct the underlying neuropathy of epilepsy.

Neurasthenia, in my opinion, more often is a purely sexual phenomenon than is generally suspected. It seemingly is due to causes which, directly or indirectly, affect the production of sex gland hormone. Long continued emotions of all kinds, especially sex emotion, produce it. Worry, cerebral overstrain, sexual desire without gratification—sometimes even sexual life without desire—sexual excess, frequent child bearing—or no children at all, after the proper age—irritation of the sexual apparatus, innutrition from any cause, all are disastrous, probably through vitiating the quality or lessening the quantity of the hormone which, in the sex gland nutritive cycle, is necessary to the structure and functioning of both the internal secretory and generative secretory gland cells themselves. Chronic infectious diseases, such as syphilis, may be assumed to act upon hormone production in two ways, viz.: 1. Worry, producing nutritive depression and perverted chemism; 2, intoxication—inhibition and perversion of function of the internal secretory apparatus. The result is profound neurasthenia. The exhaustion produced by any disease is merely neurasthenia, probably produced by internal secretory disturbance affecting the production of hormone, the natural rejuvenator of nerve energy. Possibly so called physical exhaustion is due to the same cause, and not altogether to "fatigue" toxins.

May we not believe that all the vital functions really are manifestations of hormone activity, acting upon neuron, ganglion, and nerve fibre? Other hormones are essential, but is it too much to say that the sex hormone is most important of all?

It is probable that a hormone complementary to the testicular hormone is produced by the prostate. The markedly beneficial results of prostatic massage

in sexual neurasthenia might be explained by, first, reflex stimulation of sex gland activity; second, liberation and absorption of sex hormone by mechanical pressure; third, stimulant and tonic effect of the hormone on the nervous system.

The administration of sex gland hormone via implantation possibly may prove serviceable in malignant disease. It certainly is worth trial. The germ theory of the etiology of carcinoma has not seemed to me well grounded. Indeed, I am of opinion that the nearer we come to a perfect knowledge of the internal secretions, the nearer we shall be to the true etiology and rational therapeutics of carcinoma. In any event, whatever the abnormal impulse may be, the result is perverted cell growth, and we may at least regard hopefully any remedial measure that promises improvement in cell nutrition.

To put my view of the etiology of malignant disease concretely, I believe that there is more than a chronological coincidence in the association of sarcoma with childhood and youth, and of carcinoma with later life. A disturbance of cell nutritive equilibrium from perverted quantity or quality—or both—of internal secretion—probably of the sex gland, the thyroid perhaps playing an important part—in my opinion underlies both varieties of malignant disease. The sex gland hormone theoretically should restore this equilibrium, making in effect the cells of the sarcoma older and stronger and those of the true carcinomata younger and stronger. In the light of the foregoing view of malignant disease, the theory of Cohnheim is especially apt in its application to malignant disease of early life, and to sarcoma and the softer varieties of carcinoma at any age.

The association of cancer with the approach or occurrence of the menopause, and with advancing age in the male, is suggestive of change in the sex gland hormone as the chief underlying factor. Epithelioma of the skin, especially, may be compared to psoriasis, in that a defect of nutrition due to perversion of internal secretion and localized by special factors of irritation is a reasonable underlying cause.

The role of microorganisms in carcinoma may eventually prove to be merely that of a special determining factor of perverted cell growth through the irritation produced, and no more "specific" than traumatism, which so often appears to be the point of departure for malignant disease.

Thyroid extract has been stated to have cured psoriasis. This is not surprising. The thyroid and sex gland hormones are seemingly complementary. Thyroid defect possibly may be the more important factor in malignant diseases of early life.

Diseases due to defective quantity and quality of either, or of both hormones, perhaps may be cured by either, but possibly may require a combination of both. The one thing needful in thyroid implantation may be a simultaneous sex gland implantation. It is my firm conviction that the administration of sex gland hormone by implantation—with or without thyroid hormone, as events may prove—is well worthy of trial in malignant disease. As to whether beneficial results will follow organotherapy, this naturally will be determined by factors independent of the etiology of the disease.

Case IV. *Dementia præcox, catatonic type.* Courtesy of Dr. George Leininger, Superintendent Illinois State Hospital for the Insane, Chicago; woman aged twenty-six years, family history unknown, duration of disease probably more than six years; Wassermann negative. Operation, March 8, 1914, Dr. Carl Michel and hospital staff assisting. Site of implantation, deep within the pelvis in the properitoneal space on the right side. Incision about 1.25 inch long, just internal to and slightly below the anterior superior spine of the ilium. Material used, portion of an ovary removed from woman of twenty-four years during a tumor operation, and refrigerated for thirty hours. It should be noted that a gland removed from a living subject and refrigerated is equivalent to one removed from a dead subject at a corresponding period after death—prior to beginning decomposition—save where the donor died of an infectious or an exhausting disease.

The wound healed by primary union. No rise of temperature. The case was examined on March 22, 1914. The implantation appeared to be successful. The mental status was unchanged. At the second examination, May 11, 1914, the implanted gland was apparently still *in situ*. There had been no improvement in the mental or physical status. I last examined the case, July 26, 1914. The implantation *per se* was evidently a success, although on account of its position the gland could not be palpated. The mental status was still absolutely unchanged. Even granting the potency of the method, under favorable conditions, a negative result should not be surprising in such unpromising cases as IV and V, or in such as were subsequently experimented upon.

Case V. *Dementia præcox.* Girl, aged seventeen years; courtesy of Dr. George Leininger. Duration of disease, about three years. Probably a masturbatory habit. No family history. Wassermann negative. Operation, March 8, 1914, Doctor Michel, Dr. Effie L. Lobdell, and hospital staff assisting. Site of implantation, right labium majus. Material used, the companion to the ovary implanted in Case II. This had been merely refrigerated, but not frozen, for a week in normal salt solution. A Graafian follicle had just ruptured at the time of death of subject, and the corpus luteum was beginning to form. Examination, March 22, 1914, showed that this implantation probably was a success. There had been a slight rise of temperature, owing probably to coincidental incision of redundant labia and slight resultant infection. The wound healed by primary union, but a small, apparently superficial abscess formed near the implantation site bed. This was opened and drained. The ovary still was *in situ*. May 11, 1914, the ovary still was *in situ*. There seemed to be a slight improvement in both the physical and mental status.

At the last examination, July 26, 1914, in the presence of Dr. D. W. McMillan, of Pensacola, Fla., and Dr. George Leininger, the implanted gland tissue was barely discernible on palpation. The mental condition was found to be remarkably improved. There appeared also to be considerable improvement in the patient's physical condition. So marked was the improvement in this case, that a few such apparent results could justly be regarded as probably confirmatory of the theory upon which the implantation was based.

From what is known today of the internal testicular secretion and of the influence of the ovarian internal secretions upon secondary sex characteristics and the functions of the nervous system, especially in the light of Fauser's blood diagnostic observations, the internal secretion of the ovary seems to be logically indicated, not only in early cases of dementia præcox and allied conditions in the female, but especially in certain severe cases of hysteria, the nerve wreckage that often follows complete surgical removal of the ovaries, in severe and obstinate cases of neurasthenia, and the neuropathy of the menopause.

Will such beneficial effects as may be secured by a more or less continuous dose of internal secretion incidental to successful sex gland implantation be permanent, i. e., will the result be merely temporary

stimulation rather than what may be termed "regeneration?"

Case VI. This, in a sense, is the most remarkable of all my implantation cases. Woman, aged sixty years, senile dement. At the time of the implantation she apparently was in good health, save as to her mental condition. Wassermann negative. With the double object of the possible beneficial effect of the male sex hormone in senile dementia in the female, and determining whether sex glands could be successfully transplanted for therapeutic purposes from the one sex to the other in the human being, I made a cross implantation in this case, March 18, 1914. In this case the possible effects in general of the testicular hormone on the female sex characteristics could be absolutely ignored. The gland employed was the right testis of an apparently healthy man, aged thirty years, dead of contact with a live wire. The donor had been dead ten hours when the testis was removed. The gland had been refrigerated for four days. Dr. Lee A. Stone and Dr. R. H. Rea assisted.

The gland was carefully prepared by removing the epididymis and slightly denuding the tubuli by excising four longitudinal strips of tunica albuginea about three mm. in width, extending for the whole length of the gland. The entire gland was used. A transverse incision about 1.25 inch in length was made, about four inches above the symphysis pubis, down to the aponeurosis of the recti. The wound was pocketed downward for approximately two inches, and the testis implanted at the bottom of the pocket. The fascial opening was closed with a pursestring suture of fine catgut, the skin wound with a catgut continuous suture, and the line of closure sealed with collodion and gauze.

Healing was prompt, aseptic, and afebrile. Considerable swelling developed at the site of the implantation and the patient complained of slight tenderness on light pressure. The skin was somewhat reddened after a few days, and the implantation seemed likely to be a failure—as had been expected. Much to my gratification, however, suppuration did not occur, and the case did far better, so far as the size of the mass which survived was concerned, than any other of my series of testicle implantations. March 28, 1914, the implanted gland could be distinctly outlined on palpation and was fairly movable. There was no longer any tenderness at the site of implantation. May 11, 1914, the surrounding exudate seemed to have disappeared and the gland was circumscribed, freely movable, and appeared to be as large as when implanted. July 26, 1914, the mass seemed considerably smaller on palpation; it was moderately consistent to the feel, still freely movable, and insensitive. There had been no change in the physical or mental status.

What apparently was the implanted testis in the foregoing cross implantation was superficial, accessible, apparently of no service, and a source of mental disquiet to the patient, hence it was removed under novocaine, July 27, 1914. The measurements of the excised mass were 4 cm. in length, 3 cm. in breadth, and 24 mm. in thickness at its thickest part. The gland proper was surrounded by a pseudocapsule of connective tissue and fat. The tunica albuginea clearly showed, here and there, and contained numerous small bloodvessels. Vascular attachments to the surrounding tissues were distinct, evidently at the points of denudation of the tunica albuginea. The point of severance of the epididymis was flattened and showed a broad area of vascular adhesion. The mass weighed 9.5 grams. The proper capsule of the gland, the tunica albuginea, and the connective tissue of the mediastinum showed beautifully. The substance of the mass, within the tunica albuginea, was of a yellowish color, and to the naked eye, distinctly fatty. The macroscopic and microscopic findings are shown in the illustrations (Figs. 1 to 12). Needless to say, I was astonished to find living tubuli seminiferi and ducts in addition to a more than normally rich vascular supply and a surprising abundance of interstitial cells.

From the results in this case I conclude that implanted human sex glands from either sex may survive in the tissues of the opposite sex, there being no greater tendency to necrosis, and perhaps less rapidity of degeneration than in homosexual transplantations. It is a striking fact that, before removal, the bulk and outline of the tumor and the conditions later shown in the specimen were more strongly indicative of a successful implantation than were the conditions in the homosexual experiments in either the male or the female.[16] No physiological observations were made in this case. As already noted, no mental nor physical improvement followed the implantation of the testis, but as the subject suffered a fracture of the neck of the femur about ninety days after the implantation, it would be difficult to determine whether or not the testicle hormone was of any value.

Case VII. Man, aged fifty-three years, musician, consulted me June 10, 1914. Always a hard drinker and a gourmand; no history of syphilis; Wassermann negative; history of two tappings for ascites, six years before. A diagnosis of cirrhosis of the liver was made at that time. When the patient first consulted me, his abdomen was enormously distended with fluid. Jaundice had appeared a few days previously and had become quite pronounced. No pain was complained of, nor was there any history of previous pain. On the scalp, backs of the arms and forearms, the elbows, the front of the right leg, the buttocks, and the lumbar region, were large patches of severe, typical psoriasis, from which the patient had suffered for many years. The patches on the arms were quite symmetrical, each measuring about 15 cm. long and 9 cm. wide. Those on the leg, six in number, averaged 7 cm. by 4 cm. The areas on the scalp and buttocks were of various and moderate sizes. A patch of psoriasis measuring 7 cm by 9 cm. existed on the abdomen, involving a small portion of the skin covering an umbilical hernia. Two patches on the lumbar region measured respectively about 6 and 8 cm. The subject was very weak and markedly incommoded by the enormous bulk of his abdomen. His appetite had been excellent until a few days before, since when it had rapidly failed.

June 14th, I removed nearly six gallons of dark bile stained transudate from the abdominal cavity, affording the patient great relief. The liver was now found to be greatly enlarged and indurated, showing plainly through the collapsed abdominal wall. The gallbladder was greatly distended and its walls thickened and hard. In the left iliohypochondriac region was a hard, oblong mass extending downward from the under surface of the liver for about four inches. From its location this tumor might have been either renal or omental. It could not be definitely determined that it was attached to the liver. Several hard, irregular masses were noted at the left of the median line in the umbilical region. Dr. Henry F. Lewis saw the case in consultation with me, and agreed that the case probably was malignant. There was a good sized umbilical hernia, evidently now containing only fluid, which freely flowed back and forth under pressure. This had been unsuccessfully operated upon some years ago. The urine contained bile in large amount and a small quantity of albumin, but no casts. The patient's heart was very weak following the operation and strychnine was given hypodermically for several days.

From the observations which I had already made of the apparent effects of the sex gland hormone upon nutrition, and especially upon that of the skin, and with a clear understanding on the part of the patient of the experimental nature of the procedure, I resolved to make a testicle implantation in this case. On June 19th, I implanted in the patient's right scrotal sac a testicle, with the epididymis excised, removed from an apparently healthy subject about twenty-one years of age, dead about thirty hours before from contact with a live wire. Ice had been packed around the testes for perhaps four hours. The operation was done ten hours after the removal of the testis from the dead subject, i. e., forty hours after death of the donor. The local postoperative course was uneventful for two weeks. The wound apparently healed by primary union and there was very little swelling about the site of the implantation. Until the fourteenth day the implantation *per se* seemed to have been successful.

On the third day after the implantation improvement was noted in the skin eruption. By the eighth day after operation, the lesions were so improved that they scarcely could be recognized as psoriasis. The skin of the left arm was nearly normal. The patches upon the back and

[16] In experiments on fowls, the most definite result I have thus far obtained was from an implantation of a testis of a young cockerel upon a pullet four months old.

scalp had entirely disappeared. The jaundice had improved, the blood pressure, which was low on account of the patient's debilitated condition, had increased, the pulse was perceptibly stronger, appetite greatly increased, the hemoglobin, which was approximately sixty per cent., was now seventy per cent., and there was a distinct improvement in color of the skin, aside from the lessening of the jaundice. A considerable reaccumulation of fluid already had occurred.

The white corpuscle count showed over 13,000 at the time of operation. On the second day the white count was over 21,000, falling rapidly after the third day to about what it was originally. The obvious explanation of the rapid rise and fall in the white cell count was an ephemeral reaction to a foreign body. There was at no time any noticeable effect on the sexual function, which had been in abeyance for several years.

The blood and skin conditions continued to improve and the patient grew stronger—despite an extensive reaccumulation of fluid in the peritoneal cavity—until the fourteenth day. The percentage of hemoglobin had rapidly increased to 90, and the red corpuscles, which showed 2,275,000 at the time of the implantation, had increased by the tenth day to 5,600,000, varying from day to day, but at no time falling below 4,000,000 before the close of the case.

The site of the psoriasis on the left arm and buttocks had now become practically normal, and that on the right arm and leg nearly so. The patient asserted that his teeth, which had been so tender and loose that he could not chew solid food, had become so improved that he could chew with comfort.

The scrotal skin wound, which apparently had united, reopened superficially about half an inch, about the ninth day after operation. This was apparently due to mechanical disturbance, the enormously pendulous abdomen giving rise to great inconvenience. The slight skin lesion, while indolent, as was to have been expected, presented no evidence of anything but the most superficial and simple pus infection. The fascial wound had not reopened and appeared to be soundly healed. The temperature was normal until the fifth day, when it rose to 100° F. It fell to normal within twenty-four hours. On the thirteenth day it again rose to 101° F., but by evening fell to normal and remained practically normal until the close of the case.

June 30th, I again tapped the abdomen, removing fully six gallons of fluid. Dr. M. Milton Portis and Dr. French S. Cary were present at the operation, and found the testis still *in situ* and apparently "doing well." The fluid, which at the previous tapping had been clear and about the color of moderately strong coffee, now approximated the color of normal urine and was distinctly turbid. The liver was perceptibly smaller and the abdominal tumors previously described had markedly decreased in size since the first tapping. Doctor Portis and Doctor Cary agreed that the case probably was carcinoma. Doctor Portis subsequently examined the fluid and stated that while the findings were atypical, he still thought the case probably was malignant. Doctor Portis's report of the examination of the fluid withdrawn at the tapping was as follows:

Specific gravity, 1010; large number of lymphocytes, endothelial cells and embryonal cells; bile in moderate quantity.

The shock of the second tapping was very severe and the patient rapidly failed. On the following day he began to have involuntary bowel and bladder evacuations. The slight granulating scrotal wound became infected about the fifteenth day after the operation and on the seventeenth day pus was distinctly perceptible around the site of the implantation. This was evacuated and the implanted testis was found to have been dissected out cleanly by the pus, which was distinctly saprophytic. The gland was of normal consistence and form, and on section the tubuli apparently were not softened or in the least broken down. No evidences of adhesions were perceptible on the surface of the gland. The patient became delirious and refused alimentation, marked albuminuria developed, and death from exhaustion occurred July 12, 1914.

The autopsy, by Dr. Joseph Springer and Dr. I. K. Jamison, showed a greatly enlarged, but otherwise typically cirrhotic liver. The omentum throughout was cirrhosed and enormously thickened. The fatty capsules of the kidneys were greatly thickened and indurated. So great was the induration and thickening of the fatty environments of the abdominal organs that they were with difficulty removed for inspection. The masses which had simulated malignant omental metastases had become so reduced in size that they were scarcely perceptible before opening the abdomen. On exposure to inspection they proved to be merely thickened and hardened portions of omentum. The spleen and pancreas were cirrhosed. The kidneys showed marked interstitial nephritis. I do not recall ever having met with a case with such extensive alcoholic pathology. Doctor Springer and Doctor Jamison made a similar comment. There was no evidence of malignancy. Histological examination of the liver showed typical cirrhosis. The implanted testis was carelessly preserved, and when submitted for histological study was found to be spoiled.

The foregoing case was a severe test of sex gland implantation and the apparent results upon the blood and skin were correspondingly noteworthy. As a probable index of the physiological effects of the sex hormone, the changes in the psoriatic skin were phenomenal. That the subject received the benefit of both the initial and the secondary physiological effects of the hormone is probable. I believe that the testicle elaborated hormone until the scrotal infection occurred, a period of two weeks. That any remedy whatsoever could effect such marked changes in the condition of the blood and skin in so unpromising a case as the foregoing, is remarkable. No treatment other than implantation, save attention to the bowels, was given. The changes hardly could have been spontaneous in a case in which there existed no natural tendency to improvement. The survival of the implanted testis for so long a period in a subject in which the nutrition of the tissues of the donor was so impaired is in itself phenomenal. The apparent improvement in the biliary obstruction, and the diminution in size of the liver and omental masses are merely noted as clinical phenomena, with no suggestion of any probable relation to them of action of the sex hormone. They obviously are susceptible of other explanations, which, I think is hardly true of the skin and blood phenomena.

*(To be concluded.)*

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# INTRANASAL OPERATION IN TUMOR OF THE HYPOPHYSIS.*

## *Report of a Case in a Child Nine Years of Age.*

By T. H. Halsted, M. D.,
Syracuse.

In what was probably his last contribution to medical science, Dr. Roswell Park, in an article in *American Medicine* for April of this year, made a plea for the collection of facts bearing upon the hypophysis and a cessation, for a few years, of papers dealing with theories and conclusions regarding the functions and disease of this organ until such time as the known facts could be collected, digested, and analyzed. The purpose of the report of the one case in this paper is to record the observations, and more particularly to draw attention to the direct and comparatively safe and not unduly difficult approach to the hypophysis by the intranasal route, the patient being a child under nine years of age.

Hirsch, in Vienna, has for four years been operating by this route, being the first to suggest this approach and demonstrate its feasibility on a living patient. Cushing, in this country, does very much the same operation, with the important exception that in doing his resection of the nasal septum, through which he passes on to the hypophysis, his initial incision is under the upper lip, not entering

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## Original Communications.

### GENERAL ANESTHESIA, WITH SPECIAL REFERENCE TO THE SURGERY OF THE GENITOURINARY TRACT.*


BY JAMES TAYLOE GWATHMEY, M. D.,
New York.


Before considering any special operations, let us first review inhalation anesthetics and the methods of their administration in common use, and state the general principles underlying them. We must bear in mind that the standards of a few years ago are not the standards of today, and no anesthetic or method of administration should be tolerated that is not both safe and pleasant.

*Chloroform.* In considering chloroform, we should remember that all evidences of untoward effects of this anesthetic, in both physicochemical and animal laboratories, and also clinically, were obtained under conditions that are now considered crude and improper. When a high grade anesthetic chloroform is administered, warmed, oxygenated, and with rebreathing to maintain the carbon dioxide in the blood, no unpleasantness is experienced by the patient in the induction of anesthesia, the respiration, pulse, and color are approximately normal during the administration; the awakening is the same as from a good nitrous oxide-oxygen anesthesia, and the relaxation is better. These statements have been verified in thousands of cases by users of the Roth-Drager apparatus, in which the anesthetic is warmed by constant rebreathing, and with which definite amounts of air, oxygen, and chloroform are given. Since impure chloroform as well as crude methods of administration have undoubtedly contributed to untoward effects in the past, and as Baskerville and Hamor have determined that oxidation products are entirely removed when chloroform is swept by oxygen currents through water, it is an additional element of safety to follow this procedure.

In outlining the difference between chloroform properly safeguarded and as formerly used, I do not wish to be put in the attitude of an advocate of the more general use of chloroform, but desire simply to emphasize the importance of administering it under correct conditions.

*Ethyl chloride.* A greater difference of opinion exists as to the value of ethyl chloride than of that of any other anesthetic. As, however, with animals in the laboratory, fatty degeneration follows the administration of ethyl chloride more markedly than of any other anesthetic, all authorities are practically agreed that it should not be used for prolonged operations. The only question, then, is as to the advisability of its employment in short operations and as a preliminary to ether.

As death under ethyl chloride may be caused simply by an overdose, as well as by intercurrent respiratory embarrassment, and as death from nitrous oxide is caused by a faulty technic only, it seems to an impartial observer that nitrous oxide is a safer preliminary to ether. It is universally conceded that ethyl chloride has its widest field of usefulness with children as a preliminary to ether, and for short operations.[1]

*Ether.* Ether is conceded by all writers to have the widest latitude of safety of any known anesthetic. This is not a good reason for its continued misuse, but, on the contrary, is a very good reason why the technic of its administration should be improved. As will be shown later, "straight ether" by the drop method is not the safest nor the best procedure.

The nitrous oxide-ether sequence, bridging over the second stage with its disagreeable features, was admitted to be a wonderful advance in technic, but occasional deaths from asphyxiation in some of our best hospitals are reported from time to time. Even in the hands of an expert, the pulse jumps from seventy-two to 100 and 150, the blood pressure is raised enormously, and the sensations just before losing consciousness almost invariably leave a dread of future operations. "Gas-ether" should be a thing of the past. By using oxygen, however, with the nitrous oxide, making a nitrous oxide-oxygen-ether sequence, both mortality and unpleasant sensation are eliminated, and respiration, pulse, blood pressure, and color are maintained at about normal. No new nor expensive apparatus is required to administer the ether in this way. The addition of a Y connection to the stopcock of the gas bag of any of the apparatus in common use, to which are attached rubber tubes leading respectively to nitrous oxide and oxygen tanks, with directions to give enough oxygen to prevent the patient from being cyanosed, is sufficient to make this a safe procedure, even in unskilled hands.

Where nitrous oxide is not available, the giving of preliminary medication, as will be outlined later, and the addition of two to six drops of the essence of bitter orange peel[2] upon an ordinary chloroform mask, surrounded by a towel to promote rebreath-

*Read at the annual meeting of the Section in Genitourinary Surgery, New York Academy of Medicine, October 15, 1914.

[1]Dr. Martin Ware reported at this meeting 20,000 administrations of ethyl chloride given under his supervision, with no mortality.

[2]See this JOURNAL for September 14, 1912, page 543.

ist's standpoint, he is not dealing with series of cancer cases, except late ones, after reasonable hope of radical operation is past. So far as prompt operation is concerned, his series of cases include only a few in which diagnosis is, humanly speaking, positive, but a great many in which cancer is more or less suspected. The actual makeup of such a series will vary according to the personal equation. An internist very much impressed with his responsibility and with the dubiousness of the diagnosis, may be imagined to refer for operation a series of a thousand cases, only ten of which are actually cancerous. Considering that, on the average, of all males over forty and up to about seventy-five years of age, about ten per cent. die of cancer and, of females, nearly fifteen per cent., this hypothetical series is not so far fetched as it might seem. In such a series, the vivisectional mortality would be from one up to two per cent., with allowance for senile and actual pathological changes of a general nature. Of the ten supposititious cancer cases, three would be saved, seven would end fatally, though not immediately. In other words, instead of sacrificing ten cases of cancer by neglect of operation, the total deaths would be from sixteen up to twenty-five, ten to twenty traumatically and almost immediately.

A more practical basis of a hypothetical series would be one including ten actual cancer cases in 100 instead of 1,000. Such a series, I think, corresponds quite accurately to my own actual clinical experience with hypochlorhydria, achylia gastrica, hepatic sclerosis, from 2,500 to 3,000 anemia cases, jaundice from gallstones, biliary catarrh, chronic gastric and duodenal ulcer, moderate obstipation, etc., in which the question of malignancy is seriously considered and cannot be set aside until observation has extended over a period which the surgeon would consider unjustifiably long in a case that did prove to be cancerous. It probably corresponds also to gynecological cases at the climacteric, in which the symptoms and physical signs correspond to the warning symptomatology of cancer, to similar experience along the urinary tract, etc. In such a series, the vivisectional mortality will be one or, more likely, two; the uncured cases of cancer about eight, for it must be remembered that, here, we are dealing with more marked signs and symptoms, i. e., with slightly more advanced cases than in the former hypothetical series. In other words, the results of caution and of negligence on the part of the internist are about equal.

If, on the other hand, the internist followed what appeared to be the rational course of promptly referring all cases in which the clinical diagnosis of cancer was reasonably positive, but in which the case did not appear far advanced,—and it should be remembered that, in any one man's experience, at least half of the cancer cases are advanced beyond any reasonable hope of operative cure when he first sees them—I think the following is a fair statement of ultimate results: Mistaken diagnosis (not cancer) ten to twenty per cent.; actual cancer eighty to ninety per cent. The vivisectional mortality for the noncancerous cases amounts to only a fraction, but to about two per cent. for the whole series, representing, except for this fraction, a hastening of death already ultimately inevitable. The total saving of life is somewhere between ten and twenty, according to the success of radical operation, rated between about ten and twenty per cent., plus the survival of all but a fraction of the noncancerous cases, compared with a total loss of the cancerous cases.

Now while it is obviously impossible to lay down any general rule or even to amass satisfactory statistics, since many patients will not acquiesce in the advice for operation, there seems to be good mathematical support of the policy of advising operation for cancer only in cases, which, on the one hand, can be diagnosed with a fair degree of certainty, and which, on the other hand, have not developed beyond an early stage.

354 Franklin Street.

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## IMPLANTATION OF THE GENERATIVE GLANDS AND ITS THERAPEUTIC POSSIBILITIES.

*Successful Autoimplantation of a Testis from a Subject Dead Twenty-four Hours. Other Successful Implantations of Testes and Ovaries from Dead Subjects. Experimental Implantations in Various Conditions, and Cross Implantation of Testes and Ovaries Taken from Dead Subjects.*

By G. Frank Lydston, M. D.,
Chicago,
Formerly Professor of Genitourinary Diseases and Syphilology, Medical Department, State University of Illinois.

(*Concluded from page 870.*)

The action and interaction of the implanted young gland and its senile, or even middle aged environment are worthy of serious consideration. To what extent an aged environment of nerve influence and tissue juices eventually will alter the biochemism of the implanted gland must remain an open question. That the implanted gland will benefit more or less by the improved quality of the blood produced by its own internal secretion seems logical enough. To what extent and for how long a time is problematic.

The integrity of the gland tissue and the quality and quantity of its product obviously are largely dominated by the elements on which it feeds. Implanted young gland tissue possibly may not long remain young when fed only by the blood of more mature, and especially of senile, life. Each sex gland is a laboratory; the gland cells are the workers. These workers select from the blood the materials for the elaboration of both the internal and procreative secretions. Upon the quality and quantity of these materials depend the quality and quantity of the finished product.

The end result of implantation, therefore, possibly may be merely the elaboration and absorption into the blood of a larger quantity of internal testicular or ovarian secretion than the recipient's own glands are capable of producing, this secretion eventually becoming of the same quality as the subject's own secretion. In this event the benefits derived from implantation would be only such as would result from a constant dose of a larger quantity of in-

ternal secretion, of a potency identical with that produced by the recipient's own glands. If it should prove to be true that a gland implanted in an elderly subject becomes greatly modified by its new environment—which modification should not be astonishing, for "the cell is what it eats"—then the same consideration would even more forcibly apply to a gland taken from an elderly donor and implanted in a younger recipient. The nutrition of an old, but still functioning gland probably is more likely to be improved by young blood than a young gland is to be deteriorated by old blood. This suggests more leeway in procuring material. It eventually may be shown that there are special indications for the selection of a gland from a donor of relatively advanced age as best adapted to the condition in hand.

How far the trophic influence of the relatively aged nerve supply of the implantation site may affect the permanence of implantation results would be difficult of conjecture, nor is it possible to say whether a community of nerve supply, sensory or trophic, or both, is likely to be established between the implanted gland and the investing tissues.[17]

If, however, we ever succeed in greatly impeding the wheels of time in their remorseless grind upon human life—and I confess optimism—it is most likely to be through the agency of internal secretion therapy, via gland implantation. As to what glands, or combinations of glands, will prove most efficacious, the future alone can show. The sex gland secretion seems to be the most important of all the internal secretions so far as its possible effects in increasing efficiency and longevity are concerned. Indeed, it may be a powerful stimulant to the activity of all the other hormone producing organs. In any event, senility and its control are merely a matter of nutrition.

If a complementary hormone should be found to be necessary to the full physiological action of the sex gland hormone, it may prove to be the thyroid, pituitary, pineal gland, or the suprarenal—or several of these in combination. The thyroid swelling incidental to menstruation and sexual excitation so frequently manifested in cases of hyperthyroidism certainly is quite suggestive. The profound nutritive effects of thyroid internal secretion are familiar enough. Possibly the effects of the sex hormone on the thyroid is in a sense "inhibitory," rather than complementary, the thyroid running riot, so to speak, with resulting hyperthyroidism when the influence of the sex hormone is removed. Granting this hypothesis, Graves's disease would be an indication for sex gland implantation. W. Blair Bell (42) says, in reference to correlation of the internal secretions in regard to their genital functions:

> When the reproductive functions cease and the ovaries atrophy at the menopause, the harmony between general and genital metabolism is temporarily deranged, and various disturbances may ensue. The basis of treatment is the administration of the necessary secretions. Some patients react to thyroid extract, some to pituitary, others, again, to combinations, so great are the individual variations.
>
> Strictly speaking, the ovary is concerned only in the temporary function of reproduction, and, by its hormones, of bending the metabolism of the body to its purpose. As accessory to these functions the ovary has been supposed to be responsible for the beauty of the vessel by means of which its ends are to be attained. But today one is beginning to wonder how far the ovary does influence secondary sex characteristics, and whether full secondary characteristics can be obtained by the influence of the ovary alone. There is evidence that hyperplasia of the suprarenal cortex can upset any influence that the female genital gland may possess, and can produce in a female some of the secondary characteristics of the male.
>
> Any influence the ovary has over general metabolism is, then, related to and dependent on its primary reproductive function. It probably does not influence metabolism except in so far as this special function is concerned. Removal of the ovaries may produce temporary disturbance, but this does not invalidate the view mentioned.
>
> The rest of the ductless gland system is related to the genital functions in various ways. The thyroid, pituitary, and suprarenals influence the development and subsequently preserve the integrity and activity of the genitalia. Others—the thymus and possibly the pineal—appear to prevent sexual precocity. All the ductless glands control metabolism in response to the necessities of the genital functions. In addition they adapt the whole organism to the possibility of the situation, and regulate the secondary characteristics, both physical and psychical, to suit the needs of the individual. Once, however, the reproductive organs are removed or undergo atrophy, the primary genital functions of the rest of the ductless glands cease, and the rearrangement of the metabolism that follows produces what are known as symptoms of the menopause. Contrariwise, insufficiency of the thyroid or suprarenals causes the cessation of the genital functions with atrophy of the uterus.

The possibility of sex gland implantation increasing longevity requires special consideration: A successful implantation may not appreciably alter the structure of the recipient's tissue and organs, although the effect on the skin and blood pressure of the experiment outlined in this paper is naturally suggestive. The viscera in general, and especially the heart, bloodvessels, and the nerve and brain tissues, may remain essentially the same, yet, even granting this, further senile changes should be retarded if, as seems probable, the internal secretions of the generative organs are eventually proved profoundly to affect nutrition. In brief, we may hope to retard senility even if we cannot "cure" it.

The question at once suggests itself, Might not the stimulating effect of the secretion defeat its own ends by exposing to overstrain organs—notably the heart—already senile? Possibly, even probably, it would do so, unless the increased efficiency was conservatively employed. Even if an increased capacity for long sustained and considerable muscular effort and increase in respiratory capacity should result, no one who is out of training should expect endurance of severe stress on heart, wind, and limb. I have made no test of this in my own case, but have observed a decided increase of capacity for mental labor, and a more rapid physical and mental recuperation from fatigue after moderate rest. This, of course, may be merely coincidental.

It has occurred to me that implantation is likely to give the most satisfactory results when employed at or about middle life, with the view of retarding senility and preserving efficiency, or increasing it, if it is below par. The normal man of forty years possibly, might at least retain the vigor of forty years until advanced age. The man past middle age with impaired efficiency, would be likely to have his efficiency restored. Successive implantations, of course, might prove to be necessary. It may eventually develop that implantation of the repro-

[17] The results of implantation in Cases VI and VII are interesting and important in their relations to the effects of fatal electrical shock on cell vitality in general, and possibly may have a bearing upon the possibility of resuscitation after supposed death from the electric current.

ductive glands is especially effective in young subjects with defective physical sexual and psychosexual development, and in subjects who have been traumatically deprived of the generative glands—recently in young subjects, or at any time in subjects past the age of puberty. In connection herewith it is well to remember that the effect should be more marked in young subjects in whom the chief secondary sex characteristics never have been normally developed, than in older subjects.

Granting that the method proves valuable in mental conditions, such as dementia præcox, the degree of benefit and permanence of results of sex gland implantation will depend upon:

1. The age of the patient.
2. The specificity and activity of such infective cause as may be determined.
3. The duration of the disease and the amount of secondary degenerative changes.
4. The degree to which perversions and defects of other internal secretory glands enter into the etiology.
5. The dose and activity of hormone.

The probable efficiency of sex gland transplantation in sexual perverts and inverts, in whom the normal psychical or physical, or both sex characteristics are poorly developed, at once suggests itself. Paresis seems to me to be a suitable field for experimentation with sex gland implantation, and I already have operated in two cases, in which, however, local failure prevented any possible therapeutic results. Syphilis in the donor may here be disregarded. It is an interesting question whether many of the mental vagaries and moral perversions that so often develop after middle age are not due to a lessening or perversion, or both, of internal sex gland secretion. We are wont to attribute these conditions to structural arterial changes, but the justice of this is doubtful. Future experience with sex gland implantation seems to me likely to change our views in this regard. Indeed, even where arterial changes are proved, a defective supply or vitiated quality of hormone sometimes may be the very essence of the etiology.

The possible detrimental action of the secretions of the implanted gland upon the functions of the recipient's own glands has in a way been decided by Metchnikoff's experiments. In 1898, he produced "serums" from both human and lower animal semen. He killed the spermatozoa in the serums by heat. When injected intravenously, these serums destroyed the spermatozoa through the medium of a cytotoxemia. This toxemia was temporary, the spermatozoa finally acquiring immunity. Since the experiments herein reported, examination of my own seminal secretion—July 15, 1914—and that in Case III, showed the secretion to be normal in each instance.

Obviously, if destruction of spermatozoa resulted from implantation because of toxicity of a large dose of alien secretions, the evil could be only temporary, unless the anatomical and physiological machinery of their elaboration was destroyed, and this would involve, first, impairment of testicular structure in the recipient; second, aberration of nervous supply; third, perverted blood constitution or, fourth, a combination of two or more of these conditions.

Should sex gland implantation prove to be as great an advantage in therapeutics as the author is inclined to believe, we soon will relegate certain gland extracts to the dead lumber room and use only the physiological living extracts, administering them continually via implanted gland tissue. And who shall say how far the principle may be applied if tissues from dead bodies can often be successfully used? Sex glands, thyroid, liver, pancreas, brain, spleen, kidney—it is impossible to say where vito-organotherapy will end, for it is by no means certain that all tissues have not a selective action on the blood, or a special biochemical, the fresh products of which are of therapeutic value. In brief, each tissue possibly manufactures its own special ammunition—antibodies—with which to combat disease, and even if growth of the implanted tissues should not occur, it is possible that a sufficient dose could be given and a sufficiently prolonged action secured, to accomplish valuable results.[18]

In the light of Abderhalden's wonderful work, it may eventually be shown that, by a special, selective, trophic action, every highly specialized tissue and organ of the body, whether glandular or not, elaborates an internal nutritive metabolic product—"secretion"—of its own. I would suggest especially the advisability of experimental subcutaneous administration of emulsions of fresh human brain tissue in certain derangements of the brain and nervous system, splenic tissue in certain anemias, heart tissue in cardiac disease, thyroid in hypothyroidism, kidney tissue in renal diseases, lung in pulmonary disease, liver and pancreas in diabetes[19] and of sex glands in various conditions.

Possibly the hormone of the internal secretion of glands, or certain metabolic products, elaborated by certain other tissues, is taken up by the blood, returns to the tissue, and stimulates its ordinary vital functions. This "secretion-nutrition-cycle"—if I may be so bold as to coin a term—perhaps may be necessary to the normal life of the tissue itself.

How far one internal secretion may supplement another, is a fascinating field for speculation, that already has received attention in this paper. The author is especially inclined to believe that, in certain cases, the sex gland secretion may be a powerful adjuvant to thyroid or other hormone therapy, especially where simultaneous implantation of sex glands is performed. As for extracts of glands of the lower animals, their field of usefulness probably always will be limited, while as for implantation of such alien tissues, failure naturally should be expected. *A priori* it would seem as illogical as was the old method of transfusion of blood from the lower animals—yet such implantations may possibly have a certain range of therapeutic usefulness.

In addition to the implantations already recorded in this paper the author has now (August 1, 1914), performed twelve operations in both sexes, using material that had been refrigerated from three to seven days. The cases comprised two females and

[18] In passing, it is worthy of comment as a medical curiosity that the much derided Cabanis, in the latter part of the eighteenth century, asserted that the brain was a secretory organ, "secreting thought just as the stomach secretes bile."

[19] The author has experimented in this manner with emulsions of renal tissue from a recently dead human body, on the guineapig, and on one human subject. No harm resulted, save a transitory orchitis in the guineapig. As already stated he also has experimented extensively with human brain emulsion.

eight males, suffering from various conditions, three senile dements, two cases of dementia præcox, two of epilepsy, and three of general paresis. In two subjects a double implantation was made. In one an anastomosis of the vas was performed. In one case, a male, a cross implantation was made. None of the subjects was promising, and as all were institutional cases, a discriminating selection was not practicable. Fully appreciating this, as well as other unfavorable environmental conditions which are inseparable from experimental work in large public institutions, and while hoping for beneficial therapeutic results, I feared that in all the cases the principal result would likely be the acquirement of a better knowledge of the limitations of sex gland implantations *per se,* and I was only too glad to avail myself of such material and conditions as were obtainable. The result in the majority of the operations can be recorded very briefly.

The implantations failed in all of the males and in one of the females, with varying degrees of local infection and temperature. The environmental conditions, the bad condition of the subjects, and the difficulty of preventing mentally deranged subjects from handling the implantation sites, probably had much to do with the failures, but I am disposed to charge them chiefly to the material used. Different results possibly might have been obtained if the implanted glands had been preserved by complete freezing. This, however, remains for subsequent solution. I do not believe that the results could fairly be ascribed to the heterologous source of the glands. In the part of this series of cases mentioned in my letter to the New York Medical Journal, March 23, 1914, the local conditions were favorable for some days.

The case of anastomosis in an old man of seventy-five years, a senile dement, was rather interesting. The implantation wound healed, the case was afebrile and looked very promising for about ten days, when the gland and the surrounding inflammatory area began to break down and slowly soften. On the fourteenth day I opened up the purulent collection and removed the tunica albuginea, which was all that remained of the implanted testis.[20] The gland, a little over half of which was used, had been refrigerated only four days, and as the companion organ was still *in situ,* July 26, 1914, in a female dement subject (Case VI) in whom I implanted it on the same day the anastomosis was performed, the material probably was not at fault. Anastomosis necessarily is a severe test of implantation, even under the most favorable conditions. The donor of the testis was a man of thirty years, dead ten hours from contact with a live wire.

In one of the males I performed a double scrotal implantation, using on one side an ovary taken from a mulatto woman dead eight hours of disease of the heart. The testis was from a subject dead twelve hours of a skull fracture received two days previously. The material had been refrigerated three days. The infection evidently was due to the implanted testicle, spreading to the opposite side, for when the organs were removed from the infected area on the fifth day, the ovary was still normal and adhesions were already noticeable on its surface.

The other ovary taken from the mulatto was cystic. I excised the pathological tissue, reconstructed a small ovary from the apparently normal glandular remnant, enveloping it in an adherent fragment of broad ligament, and implanted it, March 18, 1914, in the axilla of a female senile dement, sixty-seven years of age. The wound healed aseptically without any rise in temperature. May 11, 1914, the gland apparently was still *in situ.* On July 26, 1914, a small movable body, a little larger than a good sized pea, could still be felt at the site of the implantation. As there was very little gland tissue from which to reconstruct an ovary, and the donor was of a race alien to the recipient, the apparent local result of the foregoing experiment is at least noteworthy. There has been no change in the patient's physical or mental condition.

No studies of the physiological effects of the implantations were made in any of the implantation institutional cases, for reasons which should be obvious to those familiar with the unfavorable environments afforded by large hospitals for the insane, where even the most intelligent, progressive, and enthusiastic staff physicians are handicapped by overwork and scanty resources in the matter of laboratory and instrumental equipment.

All of the implantations performed were understood by the relatives of the subjects to be experimental, and were done with their knowledge and full consent.

## CONCLUSIONS.

1. At least temporarily, probably permanently—and indubitably therapeutically—successful total or partial implantation of human sex glands in both male and female is practicable.

2. Glands taken from the living subject are most desirable, though rarely obtainable. The closer the blood relationship of donor and recipient the better, but such relationship is not necessary for purely therapeutic purposes.

3. Judging by my own autoexperiments and heteroexperiments, and with due respect to Carrel's observations, I conclude that, while glands frozen before decomposition may be available, they must be used without freezing and very promptly after removal from the body, to obtain a fair average of successes. Glands taken from the healthy dead body at any time prior to the beginning of decomposition are of therapeutic value equal to that of those taken *in vivo,* if implantation succeeds. Portions of glands are to a certain degree therapeutically serviceable, according to conditions and dose.

4. Where we are not warranted in incurring risk, the subject from which the glands are taken should be selected with extreme care.

5. The ovary and the testis probably are alike in their susceptibility to implantation, both from the living to the living and from the dead to the living. If any difference exists, it seemingly is in favor of the ovary. In human beings, the gland of one sex is transplantable upon the other, and it is possible that the hormone of the one is useful to the other. My experiments apparently show that the tissues

[20] Note how this differed from the condition of the implanted testis on removal in Case VII.

of the female are more hospitable to the implanted male sex glands than are the tissues of the male.

6. The benefits of implantation probably accrue irrespective of the site of the implantation, but the vicinity of the peritoneum (extraabdominal) in the female, and of the tunica vaginalis in the male, are the sites of election.

7. The internal sex gland secretion is stimulant, nutrient, tonic, and reconstructive, and should increase resistance to disease. Certain chronic infections, notably tuberculosis, serious anemia, neurasthenia, and conditions of profound debility should be benefited by implantation.

8. The development of senility possibly can be retarded and longevity increased by internal sex secretion derived from implantation. The climacteric may be postponed by it, or the disagreeable features of the climacteric relieved.

9. Used at a very early period in the disease, internal sex secretion should theoretically be the logical remedy for dementia præcox and allied conditions.

10. The internal sex gland secretion via implantation, has a very useful field in the treatment of impotence in the male.

11. Implantation, with or without anastomosis in the male, possibly may have a certain range of usefulness in sterility in both sexes.

12. Defective and aberrant psychical or physical sex development and differentiation—inversions and perversions—are definite indications for sex gland implantation. Certain cases of cryptorchidism and imperfect testicular development are an especially promising field for it.

13. Chronic diseases of the skin due to, or modified by nutritional disturbances—notably certain types of chronic eczema, psoriasis, and ichthyosis—in a certain proportion of cases apparently are likely to be benefited, and possibly cured by sex gland implantation.

14. That arteriosclerosis will in its early stages be benefited by sex gland implantation is probable. Inferentially, if taken early, senile dementia possibly may show beneficial results.

15. All conditions incidental to sex gland mutilations in either sex afford a positive indication for sex gland implantation, the probability of benefit being inversely as the length of time that has elapsed since the mutilation, and dependent on the age at which it occurred.

16. The most important point of all is that, in properly selected cases, successful implantation ought inevitably to increase physiological efficiency, with all the benefits accruing therefrom. With increased physiological efficiency come individual and social efficiency.

17. Opportunities should be sought in the human subject for histological study of implanted glands at varying periods after implantation, to determine in what degree both generative and internal secretion gland tissues endure.

18. Every effort should be made so to amend our laws that viable tissues of all kinds, notably internal secretory glands, shall become available to science. To this end the public especially should be made to understand that the sacrifice of a portion of thyroid or of a single ovary or testis by a living subject is not disastrous. The author believes that possibly there are times when such a sacrifice would restore reason, perhaps even save life. Legislation and public sentiment should favor scientific research. Between the antivivisectionists, on the one hand, and popular reverence for the dead human body, on the other, we are in sore straits. Why should there be a waste of material which, if properly used, possibly might add so much to the health, happiness, efficiency, and even to the longevity of the human race? Let us strive for the conservation of biological energy.

As matters now stand, only persons in affluent circumstances, and very few even of these, and a limited number of the poor in our institutions can avail themselves of sex gland implantation.

## APPENDIX.

Since my first six experiments were made and the greater part of this paper was written, the author's attention has been called to some very interesting observations which, so far as they go, serve to strengthen the position herein recorded regarding the value of sex gland transplantation hormone therapy.

Leopold-Levi (43) reports a case of rheumatism and psoriasis, associated with hypothyroidism, successfully treated with thyroid extract. In another case of psoriasis excellent results followed the administration of "testicular powders."

Garré, of Bonn, has expressed himself enthusiastically over the prospects of thyroid implantation. He says:

> Transplantation of the thyroid will revolutionize the work of the social worker within a few years. Crime, idiocy, the lack of development in children, degeneracy will be lessened through the knowledge of this remarkable organ which is just dawning upon us.
>
> To the thyroid have been traced thousands upon thousands of cases of stunted growth, of mental undevelopment, of idiocy, and such defects. An undeveloped thyroid means an undeveloped child.
>
> Let us take the case of father and son. The father has a normal thyroid, and the son's is undeveloped, hence he is making no progress, mentally or physically. We can remove one third or even two thirds of the father's gland without injuring him in the least, and by transplanting this to the son can soon bring him to positive normal development.

Transplantation of thyroid from the dead to the living under proper conditions probably is quite as practicable as transplantation from the living to the living, unless, as Carrel has stated and Garré seems to believe, and contrary to my experience with the testicle, donor and recipient absolutely must be closely related.

Bandler (44) states that he has used ovarian extract with success in dysmenorrhea, the disturbances of the climacteric, atrophy of the uterus, and amenorrhea. As he usually combines iron with the ovarian extract, comment is unnecessary.

Dubois and Boulet (45) assert that intravenous injections of prostatic extract produce a fall of blood pressure, with an associated increase of brain volume and a lessening of renal tissue volume.

Iscovesco (46) notes the effects of a "lipoid" extracted from the testis and ovary. Clinical trial of this lipoid in the daily dose of 0.02 gram (one third of a grain) for thirty days in eleven patients suffering from hypochondria, or neurasthenia with sexual

weakness, and in eight aged men, resulted in increased general vigor, a better mental attitude, and improved capacity for work. In four of the eight old men the blood pressure was lowered. Vesical tenesmus, due to prostatic hypertrophy, in three of the cases, disappeared completely and permanently after an injection of 0.16 gram (two and a half grains) of the liquid. No toxic effects were noted from the large doses, either in these patients or in the animals. The author lays stress on the erythrocytic properties of the lipoid and extols it in the treatment of severe anemia, notably chlorosis, and in severe conditions of innutrition.

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## PILOCARPINE IN HIGH BLOOD PRESSURE.*

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Just what the official account[1] of pilocarpine ought to include is not clear, but certainly the first named of the two species is a very inferior drug, and its recognition is excusable only on the ground that the market is often devoid of anything better. The leaflets yield four alkaloids, constituting about 0.5 per cent. of their weight, pilocarpine, isopilocarpine, pilocarpidine, and jaborine.

Pilocarpine is the dominant alkaloid and is official, together with its salt the hydrochloride. The alkaloid jaborine differs from the others in its action, in that it resembles atropine; while the researches of Bastedo conclusively prove that the action of pilocarpine on the end of the secretory nerves is directly antagonistic to atropine, as well as its action on the nerves governing smooth muscle, the termination of the vagus, and the third nerve in the internal eye.

When applied locally in strong solution, it stimulates to a small degree the gland and muscle cells. It does not affect, however, the sensory nerve endings or the striated muscles or their motor end plates. In common with atropine, pilocarpine acts after nerve degeneration, and it is presumed that it affects a material which serves as a receptor of nerve impulses, most likely a colloid. For practical purposes we can omit the reference to the receptor, and say that it acts on the nerve endings.

In full physiological doses, pilocarpine is a powerful diaphoretic, causing a copious flow of sweat, containing an increase of solids. The reaction of the sweat is at first acid, then neutral, and later alkaline; the early acidity is probably due to the admixture of waste products from the sebaceous follicles. If the nerves between the ganglia and the sweat glands are cut, the action of the drug is not inhibited, so that its action must be on the nerve ends in the sweat glands or on the gland cells.

Pilocarpine is the antagonist of atropine; it stimulates those tissues which atropine depresses; in the presence of pilocarpine a much increased dose of atropine is required to produce its physiological action.

The action of pilocarpine is to stimulate all secretions, with the possible exception of that of the mammary gland. In the liver the production of sugar is increased, but not that of bile. The secretions most affected are those of the skin, the salivary glands, and the pancreas, but those of the eyes, ears, and stomach, with the intestines, all share very markedly in the result. There is hyperemia of the tissues, whose activities are increased owing to the direct stimulating effect on the nerve endings in the gland or of the gland cells.

The marked pupillary contraction is due to stimulation of the nerve endings of the third nerve. The vessel walls are not affected, and there is no increase of vessel tension. The terminal filaments of the vagus in the heart are stimulated and the heart action is slowed, the cardiac muscle is directly depressed by full physiological doses. The digestive processes are stimulated by the increased activity of the pancreas, intestinal fermentation is thus lessened, and toxemia, the strong factor in arterial hypertension, is decreased.

The action of pilocarpine on the skin, stimulating both the sebaceous and the sweat glands, its very beneficial action on the hair follicles, increasing the strength, lustre, and quantity; its stimulating influence on the growth of the nails, suggest a broad field for its employment more generally in cutaneous disease. To the kidneys (when used in small doses, grain 1/30 three times daily) it is a direct stimulant; the use by inunction of an ointment, containing pilocarpine, ten grains, wool fat, one ounce, rubbed well into the loins, has a favorable action in acute suppression of urine. Its beneficial action on

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[1]The leaflets of Pilocarpus jaborandi, Holmes, or of **Pilocarpus** microphyllus, Stapf (Fam. *Rutaceæ*), yielding, when assayed by the process given below, not less than 0.5 per cent. of alkaloids. *U. S. P.*